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VOLUME 69 JANUARY 1953 NUMBER 1

MESENCEPHALOTOMY IN TREATMENT OF "INTRACTABLE" FACIAL PAIN

E. A. SPIEGEL, M.D.
AND
H. T. WYCIS, M.D.
PHILADELPHIA

FACIAL pain persisting not only after application of the usual conservative methods of treatment but also after neurosurgical procedures such as retrogasserian rhizotomy and/or prefrontal lobotomy is a challenging problem.

We had the opportunity to make observations in six cases of this type in which we placed electrolytic lesions in the pain-conducting pathways at the mesencephalic level by means of the stereoencephalotome (mesencephalotomy). In some cases this procedure was combined with lesions of the dorsomedial nuclei of the thalamus (mesencephalothalamotomy[1]) in order to reduce the emotional reactivity to remaining pain sensation due to accessory pain-conducting fibers.

TECHNICAL AND ANATOMICAL DATA

Originally the punctures were performed through the superior colliculi at the level of the pineal center, or a few millimeters behind this point, in a direction parallel to the interaural plane. Recently we have chosen an oblique puncture which is inclined backward 34 degrees to the interaural plane[2] and which lies in a plane through the posterior commissure. This oblique direction of the puncture increases the probability of injuring the ascending pain-conducting pathways.

Since we found in measurements on 30 brains[3] that the interaural line[2] intersects the posterior commissure-pons line[2] at an average angle of inclination[2] of —4 degrees, a puncture at an angle of +34 degrees corresponds to a section cut at right angles to the midsagittal plane at an angle of +30 degrees to the posterior commissure-pons line (Fig. 1; line *B*, Fig. 3). The

From the Departments of Experimental Neurology and Neurosurgery, Temple University School of Medicine and Hospital.

This investigation was supported by a research grant (MH 372) from the National Institute of Mental Health, of the National Institutes of Health, Public Health Service.

1. (*a*) Spiegel, E. A., and Wycis, H. T.: Mesencephalotomy for Relief of Pain: Principles of the Method, in Anniversary Volume for O. Pötzl, Vienna, 1948, p. 438. (*b*) Wycis, H. T.; Soloff, L., and Spiegel, E. A.: Facial Pain Persisting After Retrogasserian Rhizotomy Relieved by Mesencephalothalamotomy, Surgery **27**:115, 1950.

2. The interaural plane passes through the centers of both external auditory meatuses and is perpendicular to the base line of the skull, which passes through the center of the external auditory canal and the inferior border of the orbit. The intersection of the interaural plane and the midsagittal plane is the interaural line. The posterior commissure-pons line connects the center of the posterior commissure with the posterior border of the pons. The angle of inclination of the brain is formed by the interaural line and the posterior commissure-pons line.

3. Spiegel, E. A., and Wycis, H. T.: Stereoencephalotomy, New York, Grune & Stratton, Inc., 1952.

position of the spinothalamic system in a similar plane may be visualized from Figure 2, which is taken from an article by Rasmussen and Peyton.[4] While at the level of the pineal center the spinothalamic tract lies close to the arm of the inferior colliculus, at the level of the posterior commissure the relatively much larger internal geniculate body lies lateral to the spinothalamic tract. There is less danger of extensive injury to the auditory system at the

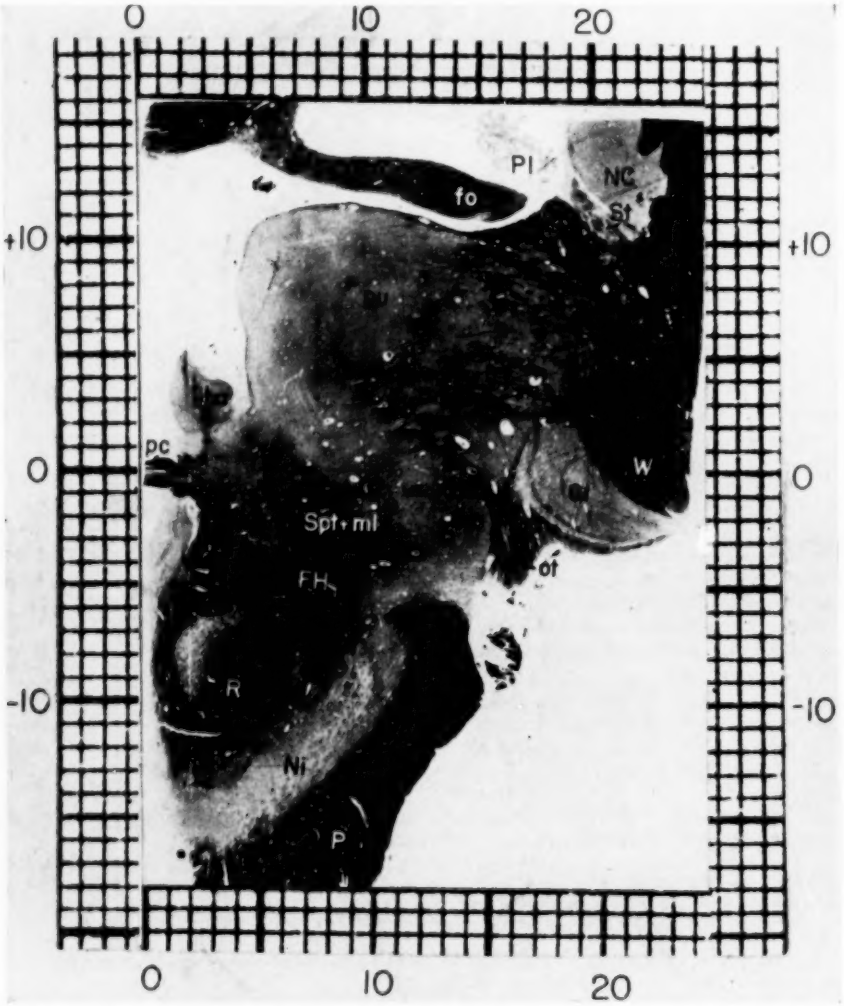

Fig. 1.—Section through the anterior part of the posterior commissure, taken at right angles to the median plane, and inclined 30 degrees posteriorly to the posterior commissure-pons line (myelin stain). The reference point of the coordinate system in Figures 1 and 3 is the center of the posterior commissure (*pc*). The scales in these two figures indicate millimeters. *FH* indicates Forel's field; *Gm*, medial geniculate ganglion; *pt*, pretectal region; *pu*, pulvinar; *R*, red nucleus; *Spt + ml*, spinothalamic tract and medial lemniscus.

4. Rasmussen, A. T., and Peyton, W. T.: Course and Termination of the Medial Lemniscus in Man, J. Comp. Neurol. **88**:411, 1948.

latter level than more posteriorly, because here the auditory system occupies a larger area than in the arm of the inferior colliculus, where a small lesion may easily interrupt all cochlear impulses.

In making such a puncture, one has, of course, to bear in mind the variability of the inclination of the brain in the sagittal direction. In our measurements, cited above, the angle of inclination [5] varied from +9 to —15 degrees. In the sagittal section represented in Figure 3 puncture lines are drawn which are inclined at angles of +19, +30, and +43 degrees to the posterior commissure-pons line; these correspond to angle of +34 degrees to the interaural plane for inclinations of the brain of —15, —4, and +9 degrees. From this figure it is evident that, despite the variation in the direction of puncture, such a puncture has a good chance to reach a system ascending a few millimeters ventral to the posterior commissure, such as the spinothalamic tract, if the puncture lies in a plane that passes through the posterior commissure. Furthermore, we have attempted to reduce injury of areas above the electrolytic zone to a minimum by producing the lesions through a single puncture instead of a row of several punctures. This is possible by introducing our stylet electrode [3] at the approximate center of the area to be destroyed. The stylet serves as the anode for the direct current and is introduced into

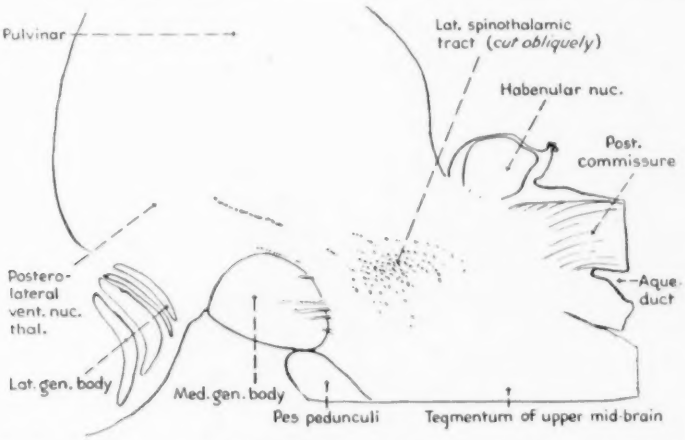

Fig. 2.—Position of the spinothalamic tract at a level corresponding approximately to the section shown in Figure 1. From Rasmussen and Peyton.[4]

the tissue in a medial, as well as in a lateral, direction, so that electrolysis on either side of the puncture canal can be performed.

REPORT OF CASES

CASE 1.—*Facial pain persisting six years after retrogasserian rhizotomy; relieved by contralateral mesencephalothalamotomy (observation period 4½ years).*

A detailed report of this case has been published elsewhere.[1b] On reexamination, in Feb., 1952, the pain had not recurred.

CASE 2.—*Facial neuralgia persisting after retrogasserian rhizotomy.*

R. C., a woman aged 59, with mild hypertensive cardiovascular disease, had had relief from apparent tic douloureux on the right side for 10 years following a retrogasserian rhizotomy (1936) on that side. In 1946 she had a recurrence of this pain. The pain came in knife-like, excruciating attacks, involving the region of the right eye and the right side of the nose and was accompanied by grimacing, as typically seen in cases of tic douloureux. Nine months prior to her admission she had a resection of the right supraorbital nerve, and six months prior to

5. The angle of inclination is called negative if the interaural line lies in front of the posterior commissure and positive if the interaural line lies behind the posterior commissure-pons line.

her admission a submucous resection was performed. These procedures, however, did not relieve her. Examination on admission revealed loss of all forms of sensation over the entire right side of the face, involving all three divisions of the right trigeminal nerve. There was also mild weakness of the right side of the face, the cause of which was obscure.

On Nov. 5, 1948, lesions were placed in the region of the left dorsomedial nucleus of the thalamus and of the spinothalamic and quintothalamic tracts in the midbrain on the left side.

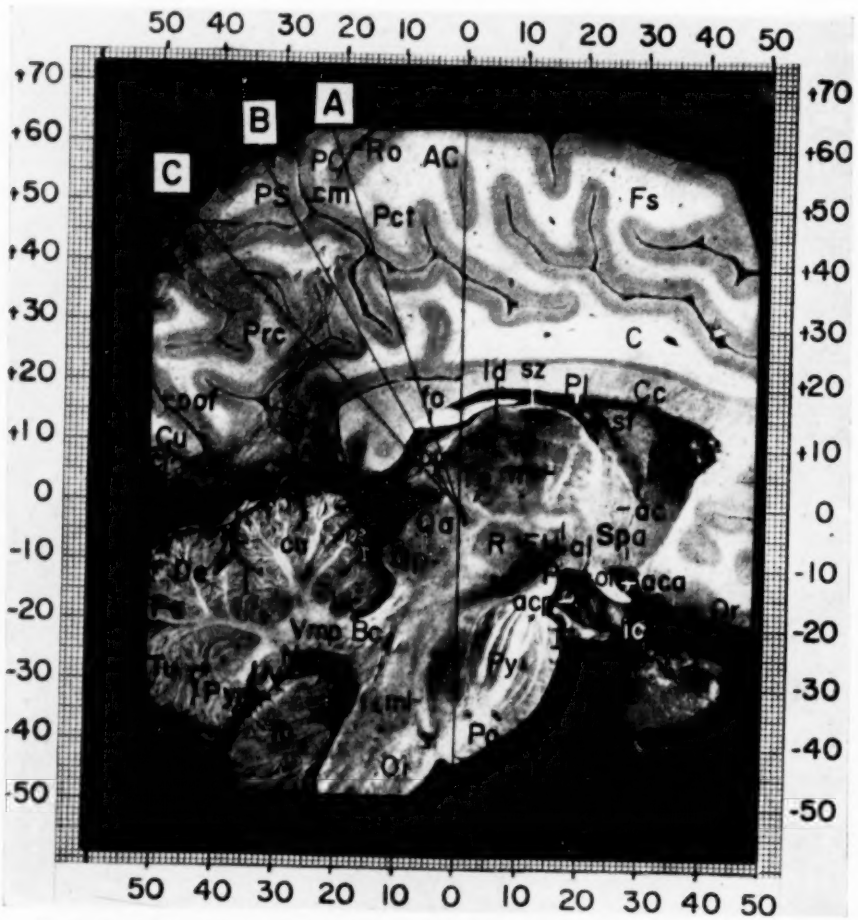

Fig. 3.—Sagittal section 5 mm. lateral to the midline. The lines *A*, *B*, and *C* indicate possible variations in the direction of punctures that are inclined by 34 degrees to the interaural plane if the inclination of the brain is —15 degrees (line *A*), —4 degrees (line *B*), or + 9 degrees (line *C*). These three punctures lie in planes passing through the zero point of the coordinate system, the center of the posterior commissure. As a consequence, despite the differences in the direction of the three punctures and their points of entrance into the cortex, their lower ends, lying a few millimeters ventral to the posterior commissure, dorsal to the capsule of the nucleus ruber (*R*), are close to each other, so that one has a good chance to injure systems ascending in this area to the thalamus.

Immediately after operation, she spontaneously volunteered the information that her pain had completely disappeared. There were distinct hypalgesia and hypothermesthesia to heat and cold over the entire right side of the body. The face was totally analgesic, as before operation.

There was mild weakness of the right leg and hand, without a Babinski or Hoffmann sign, lasting four days only. The sensory findings persisted unchanged (Fig. 4). During the first three months after operation she had only occasionally slight pain in the region of the eye and malar eminence. Reexamination at periodic intervals, the last in February, 1952, showed the sensory distribution to be unchanged. She did not complain of her former pain.[5a] On occasions she would say that her right lower extremity was colder than the left.

CASE 3.—*Facial neuralgia persisting after retrogasserian rhizotomy.*

P. M., a woman aged 62, suffered for six months from pain in the upper teeth and face on the left side (except for the forehead and eye). Extraction of the teeth, medication, and retrogasserian rhizotomy (six weeks preceding admission) failed to relieve her. After this operation the entire left side of the face was anesthetic, involving all three divisions of the left trigeminal nerve. She had also complete ptosis of the left eye, paralysis of the internal rectus muscle on

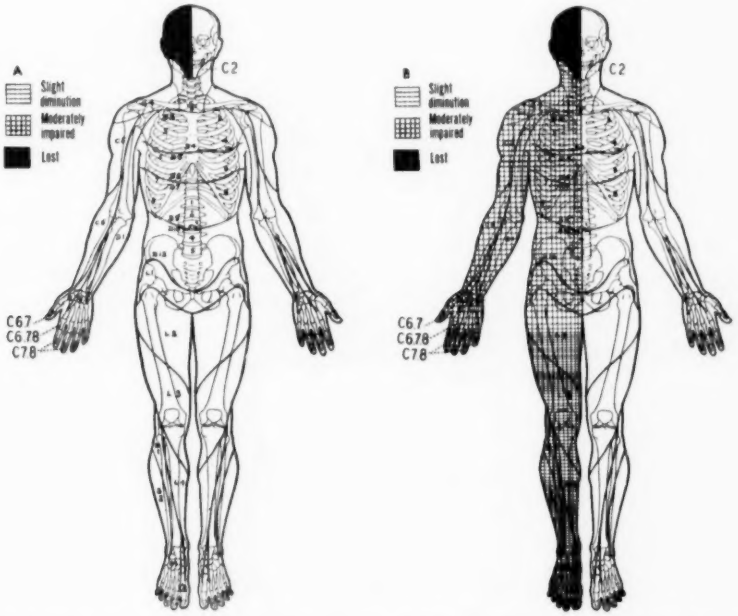

Fig. 4 (Case 2).—Pain and temperature sense distribution (*A*) before and (*B*) two months after operation.

the left side, and dilation of the pupil, without reaction to light, findings indicating that a secondary third-nerve involvement had followed the rhizotomy. Her pain persisted and became severer. She became emotionally very disturbed with her pain and was unmanageable at home.

On her admission to Temple University Hospital, the left side of the face was found to be insensitive to pain, temperature, and touch stimuli, with involvement of all three divisions of the trigeminal nerve, and there was complete paralysis of the left third nerve. Large doses of meperidine (demerol®) hydrochloride and chloral hydrate served only to confuse her and did not relieve her. She became so noisy that it was necessary to remove her from the ward and place her in a closed room. At times her confusion became so severe that she was hallucinated, and her disturbance appeared to be bordering on a psychosis.

5a. In December, 1952, the patient had an attack of facial pain, which responded to protamide® injections (a stable sterile colloidal solution of processed and denatured proteolytic enzyme for intramuscular injection).

On Nov. 8, 1951, lesions were made in the dorsomedial nucleus and in the region of the nucleus arcuatus and adjacent parts of the nucleus ventralis posterolateralis on the right side. On the day after operation the patient did not complain of her former pain; she had only a mild headache. There were definite hemihypalgesia of the body to pinprick and hemihypothermesthesia for heat and cold over the left side. The left side of the face was completely anesthetic, as was noted prior to operation. She became much quieter and was easy to manage. On Dec. 18, she was discharged to her home. Owing to a recurrence of her pain, she was readmitted (Jan. 3, 1952). At that time the hypalgesia of the body had disappeared. On Jan. 10, 1952, lesions were produced in the dorsomedial nuclei bilaterally and in the pain-conducting pathways at the level of the posterior commissure, just caudal to the thalamus on the right side. On reexamination two months after the latter operation, the patient did not need analgesics and did not complain of her former pain. Gradually, she again became noisy and confused, but always denied having pain. She died suddenly, on April 3, 1952.

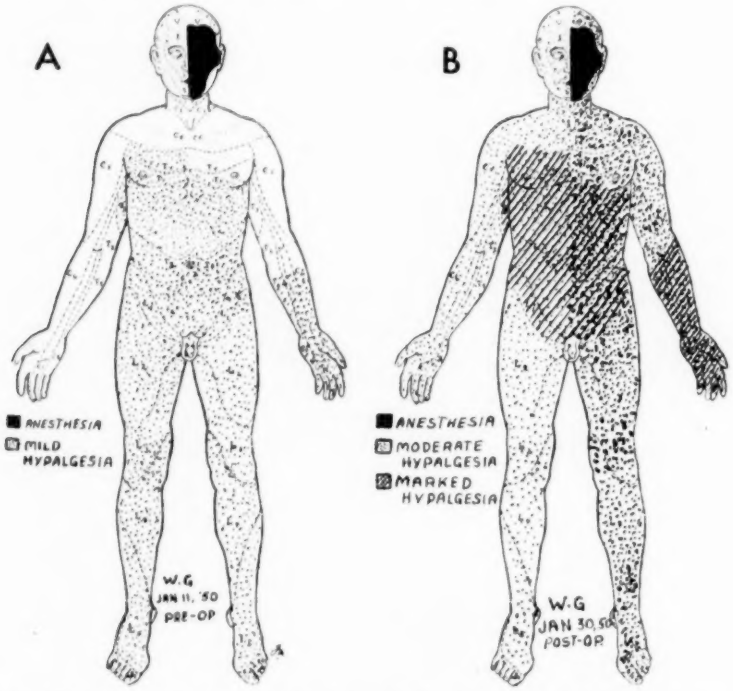

Fig. 5 (Case 4).—Pain and temperature sense distribution (*A*) before and (*B*) two weeks after operation.

CASE 4.—*Facial pain, apparently thalamic in origin.*

W. G., a man aged 45, with vascular hypertension had short-lived right hemiplegia in 1946 and left hemiplegia in May, 1947, which was also transient except for weakness of the left hand. Three days after the latter cerebrovascular accident, severe, constant, dull pain developed in the left side of the face. In addition, there were sudden, sharp pains of variable duration, occurring 5 to 10 times a day. No relief was obtained with alcohol blocks of the supraorbital and maxillary nerves (1948), left retrogasserian rhizotomy (February, 1948), four electroshock treatments (April, 1949), resection of the right cortical sensory face area (May, 1949), and left prefrontal lobotomy (October, 1949).

On admission the patient showed complete trigeminal anesthesia and hypalgesia and slight hypothermesthesia below the fifth thoracic dermatome on the left side, in the forearm and the hand on the left, and from the fourth thoracic dermatome down on the right side.

On Jan. 16, 1950, bilateral mesencephalotomy was done in the region of the superior colliculus, with the use of local anesthesia (three rows of lesions at 6, 7, and 8 mm., respectively, lateral to the midline on the right, two rows at 6 and 8 mm. lateral to the midline on the left side). Immediately after operation the patient stated that he had no pain and complained only of diplopia. The latter was due to a right hypertropia, caused by partial weakness of the left third cranial nerve. There was generalized reduction in the appreciation of pain and temperature sense throughout the entire body. This was most marked between the fifth thoracic and the first lumbar dermatome bilaterally, but was more pronounced on the left and over the distal portion of the left upper extremity (Fig. 5). Touch stimuli were appreciated throughout. Coordination, vibration, position sense, and stereognosis were good.

Six and one-half weeks after operation (March 3, 1950) his wife reported that he had very little facial pain. His only complaint was the diplopia. She also noticed that he had no taste sensation for sweet or salty substances. Apparently, the midbrain lesion had also affected the

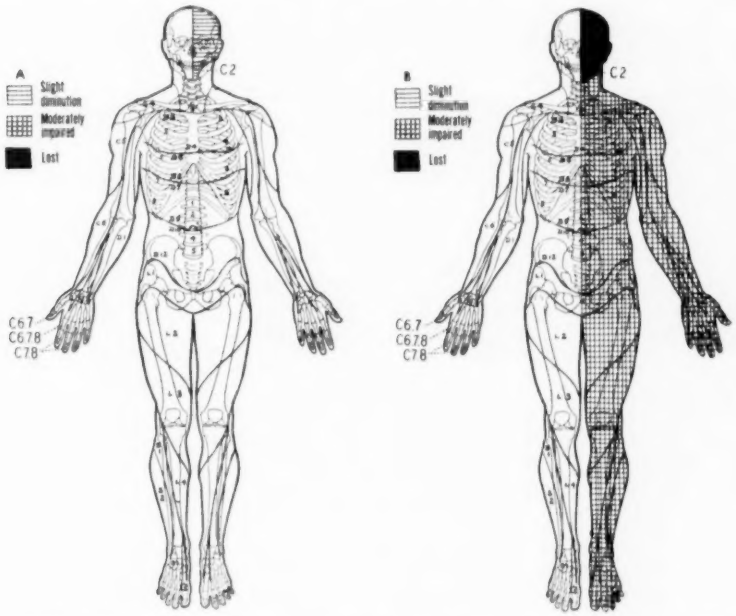

Fig. 6 (Case 5).—Pain and temperature sense distribution (*A*) before and (*B*) two weeks after operation.

fibers carrying taste sensation. In May, 1950, he still did not need analgesics. Four and one-half months after operation (at the beginning of June, 1950) the pain recurred in its old severity.

CASE 5.—*Facial pain secondary to a vascular pontine lesion.*

R. Y., a man aged 60, was well until August, 1948, when he apparently had a stroke. This began with weakness of the entire body and pain in the region of the head. He also stated that he had double vision and inability to balance himself. Three days later his right limbs began to be paralyzed; at the same time he noted paralysis and shooting pains on the left side of his face. A stellate ganglion block was performed on the left side, without relief of the pain. Within a week he recovered almost completely from the paralysis of the right side of the body. However, the pain in his face continued as before; he described it as a burning sensation. For the next year he spent practically all the time in bed. His pain kept increasing in severity, so that in September, 1949, a right-sided prefrontal lobotomy was performed. This, likewise, did not relieve his pain.

In May, 1951, he was referred to us for possible therapy. He was cooperative but emotionally rather unstable. Physical examination disclosed evidences of moderate hypertensive cardiovascular disease. His blood pressure ranged from 160/90 to 200/120.

Neurological Examination.—Pain and temperature sensations were decreased on the left side of the face. When this side of the face was stroked with cotton or touched with the hand, the patient experienced a burning sensation. The rest of the dermatomes, however, showed no sensory abnormalities. There was no evidence of motor weakness on either side of the body except for slight deviation of the tongue to the left. Deep reflexes were more active on the right than on the left. Babinski and Hoffmann signs could not be elicited on either side.

On July 5, 1951, electrolytic lesions were placed in the region of the spinothalamic and quintothalamic systems, in the most cranial part of the midbrain on the right side. Immediately after operation the patient was somewhat drowsy and confused, so that it was difficult to evaluate

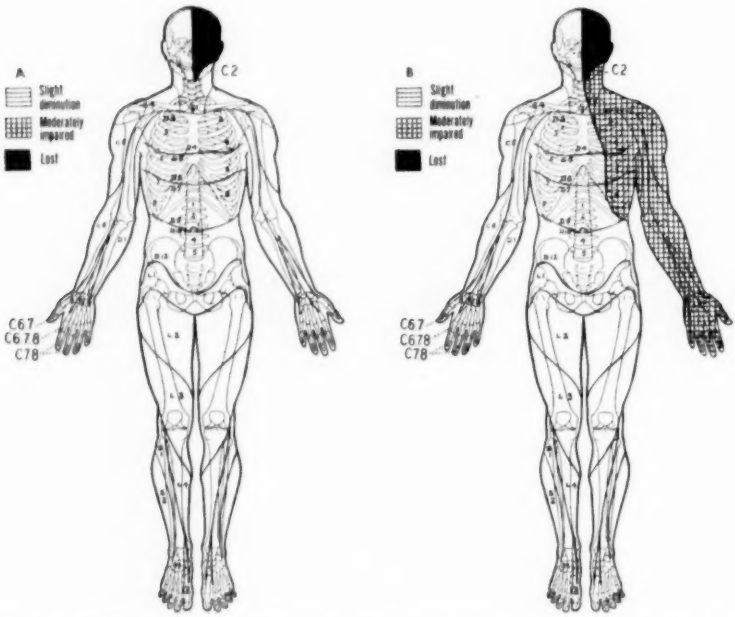

Fig. 7 (Case 6).—Pain and temperature sense distribution (*A*) before and (*B*) four days after operation.

the degree of his pain. However, within a week, his sensorium cleared, and his confusion had greatly diminished. On the 11th postoperative day and subsequently the patient was sufficiently cooperative that a definite examination of his sensory status could be made. There was definite analgesia of the left side of the face, reaching to the midline. There was also hypalgesia over the entire left side of the trunk (Fig. 6). The patient did not complain of spontaneous pain. The corneal reflexes were intact. There was no loss of sensation to light touch, vibration, or position stimuli. There was no astereognosis. Writing of numbers on the skin was easily discernible. The preoperative audiogram, recorded by Dr. Saltzman, showed peaking corresponding to the middle tones and sloping at both ends. Twelve days after the mesencephalotomy (July 17) the same configuration of the audiogram was found. There was, however, a slight rise in threshold for all frequencies bilaterally, and the contralateral ear was the more affected. In addition, the patient complained of tinnitus after operation. The patient was discharged on July 23. He was followed at periodic intervals thereafter, up to nine months after operation, when no recurrence of his former pain was noted.

CASE 6.—*Postherpetic neuralgia unrelieved by retrogasserian rhizotomy.*

C. S., a woman aged 70, had in July, 1945, a severe attack of herpes zoster, which involved all three divisions of the left trigeminal nerve. The vesicles extended sharply to the midline; scaling persisted for approximately eight weeks. All during this time she complained of a severe, burning, scorching pain. At times it was intermittent, and was relieved only by a hypodermic injection of morphine. There was no trigger area from which the pain began. The pain became so excruciating that the patient had to seek surgical relief. In November, 1945, the left trigeminal root was resected by another neurosurgeon. This gave her some relief for two weeks, when the pain again returned. At times the pain became so severe that it would cause her to scream. As a result of the scarring, secondary to the healing of the blebs, there was a severe deformity of the tissues about the left eye. In December, 1945, plastic repair was made about the left eye, resulting in a good functional and cosmetic result. Her pain persisted until the time of admission and at times was so severe that she threatened suicide.

The patient was admitted to Temple University Hospital on March 17, 1952. She was in excellent general physical condition. The blood pressure ranged from 128 to 150 systolic and 72 to 92 diastolic. The neurological status was essentially normal except for the area of the left fifth cranial nerve. There was anesthesia in all three divisions, extending sharply to the

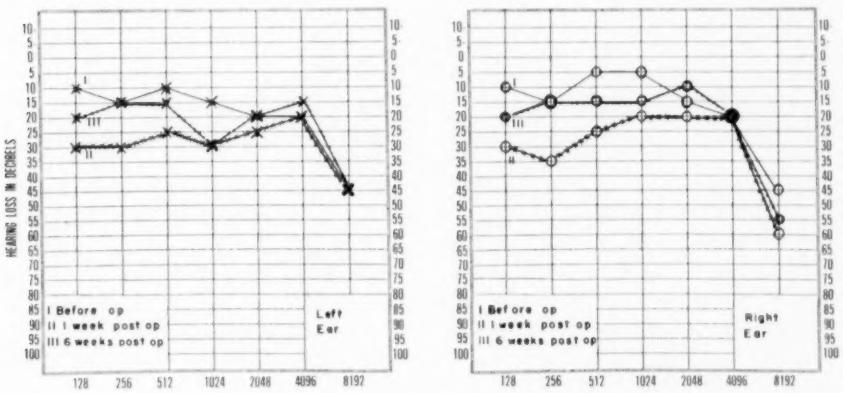

Fig. 8.—Audiometric findings in Case 6: left ear; right ear before and after right mesencephalothalamotomy.

midline. The corneal reflex was absent on the left side. The left side of the face, particularly the left side of the forehead, was scarred as a result of the herpes zoster.

On March 20, 1952, electrolytic lesions were placed on the right side in the region of the dorsomedial nucleus of the thalamus and of the spinothalamic and quintothalamic tracts of the midbrain. The patient was somewhat drowsy and confused for about three days after the operation. During the first postoperative week she was somewhat forgetful of recent events but had a good memory for old events. She did not complain of her former pain, either spontaneously or when asked about it. She complained of some pain in the right ear for several days after operation, which may have been due to the pressure from one of the rubber ear plugs of the apparatus. The left half of the face, of course, remained anesthetic, as before operation.

Examination four days after operation revealed in addition definite hypalgesia and hypothermesthesia, particularly for heat, on the left side, extending over the neck, upper chest, and arm (Fig. 7). Threshold values for pain tested with a spring algesiometer were expressed in grams, as tabulated.

	Threshold, Gm.
Right side	2
Left side	
Neck	$>15; <20$
Shoulder	12
Forearm	6
Wrist	2-3
Fingers	10

There was no definite difference between the left and the right side in the threshold for touch sense, as tested with von Frey hairs. Localization of touch stimuli, recognition of numbers written on the skin, and vibration and position senses were equal on the two sides. Two-point discrimination was definitely impaired on the left arm; e. g., in 16 tests with the two points 6 cm. apart, the double nature of the compass points was correctly recognized 12 times on the right forearm and 7 times on the left forearm.

The patient was discharged 12 days after operation, free of facial pain. An audiometric examination before operation revealed good tone appreciation in both ears, and there was no evidence of tinnitus. Seven days after operation the audiogram (Fig. 8) showed a slight deterioration of auditory acuity for low and middle tones in both ears, and there was a moderate lowering of threshold of discomfort for the middle and high tones, which was more pronounced in the left ear.

On reexamination (July 1, 1952), the patient was still free of the facial pain, only sometimes she had dysesthesia in the left eye, and occasionally a feeling of "being pinched" in the left cheek. There was still hypalgesia over the shoulder, the upper part of the chest, and the arm on the left side, besides the anesthesia of the left side of the face. The audiometric findings were slightly improved (Fig. 8).

COMMENT

In the first three cases of this series a diagnosis of tic douloureux had been made by the patients' physicians, and the typical retrogasserian rhizotomy had been performed. This operation apparently was technically successful in so far as it resulted in complete anesthesia of the corresponding side of the face. However, the pain persisted in Case 1 for six years, and in Case 3 for several weeks, after the retrogasserian rhizotomy. In Case 2 the pain returned 10 years after this operation and had been present two years before the mesencephalotomy was performed. In Cases 1 and 2 lesions of the pain-conducting systems at the mesencephalic level and of the dorsomedial nucleus were produced on the opposite side. This procedure resulted in relief of pain, observed postoperatively in Case 1 for 4½ years and in Case 2 for over three years.[5n] In Case 3 a lesion of the opposite ventral and dorsomedial thalamic nuclei had only a temporary beneficial effect. Additional lesions of the contralateral pain pathways at the mesencephalic level and of both dorsomedial nuclei resulted in relief of pain. The time of observation in the latter instance is too short to permit a definite conclusion. The appearance of hypalgesia and hypothermesthesia in areas opposite the lesion indicates that the spinothalamic system had been injured in these three cases. Whether the quintothalamic fibers also were injured cannot be stated with certainty, since anesthesia of the face existed before the mesencephalotomy, owing to the section of the fifth nerve. The sensory disturbance may sometimes reach the midline (Cases 1, 2, 5); sometimes it is incomplete (Case 6). In Case 2 it is apparently permanent; in Case 1 it was transitory.

The regression of the sensory disturbances produced by the electrolytic lesion, e. g., in Case 1, may have various causes. The lesions may have interrupted only part of the fibers of the spinothalamic system, and a zone of edema surrounding the electrolytic lesions may have impaired the conduction of impulses in the remaining fibers. With the regression of this edema the function of the remaining fibers of the spinothalamic system may have been reestablished. One also has to bear in mind that accessory systems (homolateral fibers of the spinothalamic tract, fibers in the reticulate substance) may compensate for the loss of the contralateral spinothalamic tract, as is known from cases of anterolateral chordotomy with anatomically

apparently complete section of this system. Which of these factors played the deciding part in our material cannot be stated, since we do not have anatomical controls.

The experience that relief of pain in the face may persist for years after mesencephalotomy, as in Case 1, although the hypalgesia produced by the lesion has regressed, at least in dermatomes outside the trigeminal area,[6] raises another problem that cannot be definitely answered. Some factors may be mentioned which may have played a part, individually or in combination. A convenient explanation would be that the pain was of a hysterical, psychogenic nature and that the operation had a psychologic effect, rather than acting on central pain mechanisms. It should be pointed out, however, that the patients were originally seen by experienced neurosurgeons, who apparently diagnosed the condition in the first three cases as typical tic douloureux and on this basis performed a retrogasserian rhizotomy. However, it should not be denied that in these cases a more or less definite emotional lability did exist; this was not the cause, but rather the effect, of the intense pain to which these patients were subjected for years. In view of this emotional component, the lesion of the dorsomedial nuclei was added to the interruption of the pain pathways, in an attempt to reduce the emotional reactivity to remaining pain impulses reaching the higher centers. Thus, we tried to interfere with the same frontothalamic circuit that Freeman and Watts [7] interrupted by means of prefrontal lobotomy in cases of so-called intractable pain, but in our cases without affecting other connections of the frontal lobe.

Besides the influence of the operation upon emotional factors, the significance of the interruption of centripetal impulses should not be overlooked. The possibility should be borne in mind that in some cases of pathologic overexcitability of parts of the central pain mechanism afferent impulses may play an important part in maintaining this pathologic state, and that even their temporary elimination may suffice to restore a normal state of excitability. Another possibility to be considered is the preoperative existence of a vicious circle; e. g., the pain could induce vasospasms, and these, in turn, could aggravate the pain; the operation may have interfered with this vicious circle. A final answer to these problems does not seem possible at present and will depend on further studies.

The importance of centripetal impulses in the mechanism of the type of pain seen in the thalamic syndrome is illustrated by Case 4. In this case the pain on the left side remained uninfluenced by homolateral retrogasserian rhizotomy, resection of the contralateral cortical sensory face area, and left prefrontal lobotomy. The pain disappeared for several months after interruption of the afferent pathways in the midbrain. This observation is in agreement with findings of Frazier, Lewy, and Rowe,[8] who were able to relieve thalamic pain by bilateral anterolateral chordotomy in the cervical portion of the cord, supplemented by blocking of the fifth cranial nerve; the pain recurred also in their case. These observations suggest that

6. The immediate, as well as the later, effects of the mesencephalic lesion upon the sensation in the trigeminal area could not be ascertained, since all patients except the fifth had been subjected to retrogasserian rhizotomy preceding the mesencephalotomy.

7. Freeman, W., and Watts, J. W.: Pain of Organic Disease Relieved by Prefrontal Lobotomy, Lancet **1**:953, 1946.

8. Frazier, C. H.; Lewy, F. H., and Rowe, S. N.: Origin and Mechanism of Paroxysmal Neuralgic Pain and the Surgical Treatment of Central Pain, Brain **60**:44, 1937.

the bombardment of the diencephalon by afferent impulses plays an important part in the mechanism of this type of central pain. The return of the pain in our case may be due to the fact that we produced a complete lesion of the ascending pain-conducting fibers in the mesencephalon on the side of the affected thalamus only, while on the opposite side the lesion was incomplete, so that impulses crossing in the posterior commissure could enter the diseased diencephalon.

The last two cases (Cases 5 and 6) have in common the apparent origin of the pain in the rhombencephalic sensory nuclei of the fifth nerve—in Case 5, due to a vascular process; in Case 6, due to extension of the inflammation from the gasserian ganglion to the pons. In Case 5 a contralateral prefrontal lobotomy, and in Case 6 a retrogasserian rhizotomy, did not influence the pain. In both cases relief was obtained by contralateral mesencephalotomy, which in Case 6 was combined with a contralateral lesion of the dorsomedial nucleus. In Case 5 observation could be made for nine months after operation; in Case 6, to the time of writing, for a few months only. Apparently, in these two cases we succeeded in interrupting the quintothalamic tracts in the midbrain. In Case 5 this may be inferred from the appearance of analgesia in the face, while in Case 6 the preceding retrogasserian rhizotomy had already produced an anesthesia of the corresponding side of the face. In Case 5 the disturbance of sensation following mesencephalotomy extended upon the corresponding half of the body; in Case 6, upon the arm and the upper part of the chest. This is in agreement with Walker's[9] findings in monkeys that at the mesencephalic level the quintothalamic tracts lie close to the pain pathways from the upper spinal segments.

Side-Effects.—In Case 5 there were confusion and drowsiness for one week after unilateral mesencephalotomy, and in Case 6, for three days after unilateral mesencephalothalamotomy. In the latter case the patient had also slight difficulties in remembering recent events for one week.

In Case 1 for several weeks there was mild impairment of the movements of the toes and ankle of the right foot, with ankle clonus and slight tremor, chiefly of the right hand when holding objects. In Case 2 there was weakness of the right hand and leg for four days. In Case 4 the patient complained of diplopia, which was caused by right hypertropia.

Disturbances in the function of the posterior column-medial lemniscus system, as a rule, were slight and transitory. In Case 1 there was slight impairment of light touch and vibration sensation on the side opposite the mesencephalothalamotomy. On the affected side the patient was also unable for some time to recognize upward movements of the large toe on the right foot. The only disturbance in posterior column function that was demonstrable three months after operation was slight impairment of tactile localization on the affected side. In Case 6 the only sign of disturbance of posterior column-medial lemniscus function was impairment of two-point discrimination.

In Case 4, in which mesencephalotomy had been performed bilaterally, there developed loss of taste sensation for sweet and salty substances.

9. Walker, A. E.: Relief of Pain by Mesencephalic Tractotomy, Arch. Neurol. & Psychiat. **48**:865, 1942; Somatotopic Localization of Spinothalamic and Secondary Trigeminal Tracts in Mesencephalon, ibid. **48**:884, 1942.

With regard to auditory disturbances, no statement can be made in two cases, because in Case 3 the preoperative confusion precluded an audiometric examination and in Case 4 the patient showed on admission a profound bilateral perceptive deafness. There was no demonstrable change in the auditory acuity in Cases 1 and 2. A slight postoperative rise in threshold was observed in two cases—in Case 5, for all frequencies, particularly in the opposite ear, and in Case 6, for low and middle tones. In Cases 1 and 5 transitory tinnitus appeared, and in Case 6, a moderate lowering of the threshold of discomfort for middle and high tones, particularly in the opposite ear.

These side-effects, most of which were transitory, do not seem serious, particularly in consideration of the relief from pain, which had been refractory to all other methods of conservative and surgical treatment.

SUMMARY

In six cases of "intractable" facial pain electrolytic lesions of the pain-conducting pathways were placed in the midbrain (mesencephalotomy), alone or combined with lesions of the dorsomedial nuclei (mesencephalothalmotomy). In three cases, in which the apparent diagnosis was tic douloureux, retrogasserian rhizotomy had been performed by neurosurgical colleagues; in a fourth case thalamic pain had been refractory also to cortical operations; in the fifth case pain of pontine origin had persisted after contralateral prefrontal lobotomy. In the first three cases contralateral (Cases 1 and 2) or bilateral (Case 3) lesions of the dorsomedial nuclei were added to the mesencephalotomy in order to reduce the emotional reactions accompanying a possible remaining pain perception. In the cases with organic thalamic (Case 4) and pontine (Case 5) lesions mesencephalotomy alone was performed. Freedom of pain for the duration of observation was obtained in Case 1 (4½ years) and Case 5 (for 9 months). In Case 2 a transitory relapse occurred after over three years. In Cases 3 and 6 the postoperative period has been too short to permit arrival at a definite appraisal. The thalamic pain (Case 4) was relieved for only 4½ months, probably owing to incomplete interruption of the pain-conducting systems; this case shows at least the important part played by afferent impulses in the pathogenesis of thalamic pain.

LANGUAGE BEHAVIOR IN MANIC PATIENTS

A Qualitative Study

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A PREVIOUS publication [1] reported some quantitative characteristics of the structure of manic speech. Function, as revealed by the pattern of language, is the focus of the present study. Judgments of design, motivation, relationships, intensity, and value become inseparable from even the simplest observations made upon language as a unit of behavior, as distinct from those made upon language as a codified system of signs. Hence these observations are presented as an attempt to differentiate various aspects of language behavior, and are a preliminary approximation rather than an exposition of fact.

Language is both a highly flexible and, at the same time, very rigidly determined form of behavior. While it varies sensitively with the individuality of the speaker, it bears also the impress of a pattern that transcends the individual and reflects the common denominators of mental and emotional states.

The pattern of language behavior in patients who develop a manic type of reaction is recognized as showing, in addition to individual variants, certain common features. These have been designated as increased verbal productivity, loquaciousness, pressure of speech, irrelevancy, incoherence, distractibility, flight of ideas, play upon words, clang associations, and circumstantiality. Some reports in the literature indicate subtler characteristics belonging to the language pattern. Stockert,[2] in a comprehensive, but rarely cited, study of language of psychotics, has made significant contributions, among them the observation that grammatical structure is longer retained than logical relationships. He noted that in the manic patient the "guiding idea," or total concept, was lost and suggested that distractibility and associations enter in to compensate for this defect. He further developed the thesis that associations are actually slowed down and that they are conditioned by affect. Newman and Mather [3] noted the following features: tendency to employ an "ele-

This paper is one of the series on language. Dr. Stanley Cobb has given helpful criticism.

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1. Lorenz, M., and Cobb, S.: Language Behavior in Manic Patients, A. M. A. Arch. Neurol. & Psychiat. **67**:763-770, 1952.

2. Stockert, F. G.: Über Umbau und Abbau der Sprache bei Geistesstörung, Abhandl. Neurol. **49**:1-82, 1929.

3. Newman, S., and Mather, V. G.: Analysis of Spoken Language of Patients with Affective Disorders, Am. J. Psychiat. **94**:912-942, 1938.

vated style," use of relatively intense and extreme words, richly elaborated sentences with a variety of syntactic devices, use of complete predication rather than phrase statements, and fondness for employing personal names, place names, dates, and other particularized references. Fromm-Reichmann [4] found that the reports of patients with manic-depressive psychosis are stereotyped and diagrammatic and show lack of subtlety and a tendency to oversimplification. Lorenz and Cobb [1] have shown that repetitiveness and redundancy, as well as impoverishment of descriptive terms, can be quantitatively demonstrated.

METHOD

The purpose of the present investigation was to apply to recorded interview material (spontaneous speech samples) a systematic analysis, outlined below. This was done on the hypothesis that, since language constitutes a spontaneously chosen, large segment of behavior in these patients, some pattern or trends might be discernible that could be correlated with other aspects of clinical information.

For convenience in grouping a heterogeneous number of descriptive elements, the artificial categories of pragmatics, syntactics, and semantics were found useful. These terms are employed in a broad, rather than strictly formal, sense. The definition used is the following: pragmatics, referring to the intentions, attitudes, and expressive behavior involved in communication; syntactics, the relationship of words and sentences to each other; semantics, the content and meaning of what is said.

The classification of the specific points listed under each of these headings is open to challenge. But language has many interrelated aspects and determinants and resists rigid schematization. The same difficulty presents itself in selection of patients. A hypomanic or manic mood swing can assert itself in an obsessive, hysterical, or schizoid patient, as well as in one with the classically described manic-depressive syndrome. For the purpose of this study 10 patients were selected, primarily upon the clinical criteria of hypomanic or manic reaction, secondarily on the basis of the formal diagnostic category of "manic-depressive" psychosis. One recorded interview, representing the spontaneous speech production of each of these patients, was carefully scrutinized for evidence of the characteristics noted below.

OUTLINE FOR ANALYSIS

I. Pragmatics

A. Awareness of interviewer: Personal comments. Use of second person pronoun. Direct or implied questions. Directives. Imperatives. Attitude: unaware to, indifferent to, hostile to, friendly. Is interviewer incorporated into preoccupations, fantasies, or delusional system of the patient? Does patient assign any role to interviewer?

B. Attitude toward what is said: Distractibility. Reference of pronouns to antecedents. Quotations: direct and indirect. Particularized references: naming, listing, itemizing, elaborating.

C. Expressive behavior—personality traits: qualification, descriptive, or quantitative. Reference to feelings, emotion. Speech mechanizations. Words denoting emphasis and exaggeration. Hesitancy. Repetition. Style.

II. Syntactics

A. Grammatical structure: loose, disjointed, fragmentary to intact; easy, casual to formal, stilted

B. Tense: subjective orientation in time—preoccupation with past, present, future

C. Negation

4. Fromm-Reichmann, F.: Intensive Psychotherapy of Manic-Depressives: A Preliminary Report, Confinia neurol. **9**:158-165, 1949.

D. Logical consistency: individual sentences: relationship of words within sentence to each other. Consecutive sentences: use of connectives, kind of relationship expressed. Objective achieved or lost. Is a thought or idea expressed that can be reformulated?

III. Semantics

A. Content—bizarre or factual

B. Emergence of theme or area of preoccupation

C. Self-evaluation

D. Insight into illness: awareness; denial or acceptance

E. Vocabulary: word choice; conventional to highly individual; prosaic to imaginative; precise to vague; metaphors and similes

DESCRIPTIVE ANALYSIS OF DATA

I. Pragmatics

A. Observations.—1. Awareness of Interviewer: This is indicated in language behavior through direct reference, personal comments, questions, directives, and imperatives. In using direct reference, each patient shows a fairly strong tendency to adhere to one predominant pattern. One used mainly such phrases as "What would you suggest," "Correct me if I'm wrong," "With your permission," "What do you think?" and variations upon this theme of extracting approval, direction, support. Another patient used almost exclusively, "You see" and "You know," pointing his remarks directly to the interviewer. This patient conducted himself as if he and the interviewer shared a precious conspiracy to which he held the key. Personal comments on the whole ignore the social inhibitions which ordinarily govern conversation. They vary from the innocuous to an astute predilection for sensitive areas. The comment, although personal in nature, is practically never followed by any indication of awareness to the reaction of the target. Not infrequently the comments are suggestive of projection of affect. The specific target is less important than the diffuse nature of the prevailing emotional tone. One angry, hostile patient employed sarcasms freely, apparently including the interviewer among her other targets.

Questions are frequent. They are almost invariably rhetorical or corroborative, rarely for specification. Again, there is nothing in the subsequent flow of talk to indicate expectation or awareness of an answer. Directives and imperatives, "Let's start from here," "You do the talking," and similar comments are plainly not followed beyond being expressed. The prevailing attitude toward the interviewer seems to be one of awareness without evidence of response.

2. Attitude Toward What Is Said: Distractibility is not invariably exemplified in language. Interruption of the stream of talk with adventitious observations occurs in some patients. In an equal proportion, absorption in the act of talking is complete for long periods without any reference to extraneous stimuli. When they do appear, the placement in the stream of speech often suggests that they appear as a punctuation point, to fill in what would otherwise have been a gap in the flow of talk.

The reference of pronouns to antecedents varies from clearness to obscurity. This seems to parallel the degree of general disorganization more than any other factor.

A very striking feature is the frequent use of direct and indirect quotations. Oftenest these appear in connection with a preponderantly anecdotal type of content.

One patient's half-hour of talk is adequately sampled by the following quotations: "And he said: 'You'll be proud of me now,' and I said: 'Why?' 'Well,' he said, 'I got what I always wanted; I'm on the band . . . and you're going to sit on the platform with me and meet everybody.' I said: 'You take another think . . .' And he said: 'You're a great disappointment to me,' and I said: '. . .'" This particular excerpt presents in pure culture, as it were, a language trait that is frequently found to a less degree in many patients. A frequent use of indirect quotation is one which refers to some judgment made of the patient by another person: "Well, I've been told . . . that I'm inclined to be a little bit stubborn." "George used to say . . . Mom is the best egg in the world, a little on the hard-boiled side . . . and." "When they were beginning to say I was excited again." The incidence of direct and indirect quotations is high both for individual patients and for the group as a whole.

Another feature that stands out by frequency of recurrence is the tendency to use particularized references, e. g., naming, listing, itemizing, and elaborating. The patient refers to a person not simply as "Miss K," but as "Miss K, the dean of residence"; not to "a skirt," but to "a skirt which is a nubbly knit"; not to "Dr. B" but to "Dr. B, who is now at N, and was formerly at the ——— Hospital." Names of persons—less so, place names and dates—seem to seed the spontaneous productions of these patients. The conversation of one patient with a chronic hypomanic state consisted almost entirely of reference to persons, families, places: "His mother was a Greenwood of Greenwood, and his uncle, John Greenwood, had a very good choice. He married Mrs. John Hopper, and her people are the Grays of the other side." This went on interminably. Again, the example given is an exaggerated use by one patient of a tendency found frequently in the language of many of the patients. This dalliance with proper names and dates is sometimes presented in such a way, at first hesitant and doubtful, then with emphasis, as is seen in ordinary experience when one insists on remembering a date or name which threatens to elude one.

The tendency to complete a list, to itemize, once a subject is mentioned seems to be fairly common. Again, one patient showed this to a striking degree. Within a few sentences the following phrasing was included: "I've been for a walk; I've done exercises over in the gym, knitted, crocheted, read, visited. . . . I had no pain whatever, not in my head, my eyes, my ears, my knees. . . . I took seconal, nembutal, phenobarbital, never tonics." Another patient said: "It is only since Jung, Adler, and Freud, perhaps 50, 60, 70 years ago . . . case histories, examples, and numbers and multiplications and variations and extremes that sound good."

Often what appears at first sight as elaboration of a topic is found to be a pseudoelaboration, merely a reiteration in slightly altered form of the same idea. "You can smile and you can frown, and I always figure that a smile is a frown upside down. So I figure if you can smile you can frown and vice versa." This occurs at all levels, in sentences as noted above, in topics of an interview, in themes of successive interviews.

3. Expressive Behavior: Another feature that stands out in the all-over language pattern is the paucity of qualitatively descriptive adjectives. Descriptive adjectives are, of course, present, but rarely of the kind which qualifies by adding subtlety or discrimination. It is true that not every speech sampling is lacking in colorfulness, but this seems to be the rule, rather than the exception. It also appears that the

impression of vividness appears during the phase of more acute disturbance and excitement and is related to the apt and uninhibited use of nouns and expletives. By contrast, the production of the chronic hypomanic patient often appears dull and monotonous. It is only occasionally punctuated by interjections or expressions that refer to current emotions.

There is a strong tendency to introduce mechanizations of language, such as stock phrases and stereotyped formulas. One patient relied heavily upon "I think," and the following quotation is characteristic of her production: "I think there should be some other way of getting it out of you, because *I think* that something deep-rooted would be something. For my own opinion, really, *I think, I think* neither myself nor anyone else knows what happened back in December. . . ." The choice of such phrases is not accidental. In this particular patient, the clinging to an intellectual, rational mode of handling life's problems constituted a strong defense for an infantile and continuously thwarted emotional need for dependence. The patient previously referred to used "you know" and "you see" in the same repetitious, mechanical way. The confused, almost incoherent content of his conversations made this phrase stand out in bold relief, as if it were an attempt to contradict the obvious inability to make anyone know or see. Another patient, equally incoherent and seemingly indifferent as to the effect of her monologue on the listener to the extent of absence of any discernible reference of pronouns to antecedents, liberally interspersed her talk with "You see," "You see what I mean," "You know what I mean." Certainly, these speech mechanizations are not unique with manic patients. However, it must be noted that these and similar ones recur repeatedly in the language pattern of many of these patients and in some are utilized to such a degree as to overshadow the more differentiated content of the flow of speech. One may also note in passing that the "normal" subject who emphasizes the "I know," "I think," in the texture of his conversation or uses other clichés with great frequency very often has an all too transparent need for his particular emphasis.

An undertone of emphasis and exaggeration is often given by a preponderance of adjectives and adverbs of degree—"*absolutely* believe," "*much* nicer," "*never* sick." Always, never, absolutely, really, of course, very, all—words with a strong emphasis—appear to occur more frequently than such words as perhaps, maybe, some, few—words suggestive of uncertainty, hesitancy, or limitation.

Hesitancy and uncertainty as to what is to come next in the stream of talk, often obscured to the listening ear by the rapidity and pressure of speech, are none the less noted when the recorded interview is reviewed. "And uh I've lost the thread of my discourse. How far had I gone? He—uh—oh, yes, uh—and then I, I . . ." One patient relied on "uh," "uh—oh—uh," in practically every sentence. Again, although not specific for manic patients, these crutches would seem to occur more frequently than is apparent when one relies upon listening alone. A hesitancy in finding the right name of a thing is not infrequently noted. This often occurs, as previously indicated, in dwelling upon place and personal names and dates. "I always thought she was a widow widower widow, how do you say it, anyway, without a husband." "I'm civil service one-of-those-things." This may account also for the increased use of demonstrative pronouns, "something," "that," "it." Sometimes approximations are substituted when the name does not come to mind—for example, "the metallic item," to refer to a copper ash tray.

Another mechanism suggestive of a play for time is the frequent repetition of a word or phrase, as though the patient was not certain of the words that are to follow. "Because he didn't, he didn't even ask me; he didn't ask me to cough." In one way or another, some mechanism is revealed by careful scrutiny of the patient's language pattern, through which time is gained before a transition to another thought is made. Sometimes transitions are abrupt, but not always. Despite verbal fluency, an impediment to progression in the development of a topic seems to occur not alone at the level of associations (which will be discussed presently) but in the mechanics of speech itself.

Style not only often persists but becomes exaggerated, and almost a caricature of the patient's ordinary mode of expression. One may see what is ordinarily a slow, deliberate, formal way of speaking exaggerated into a pompous, oratorical, and declamatory style. This was noted in two patients known to the interviewer during periods of mood swing and relative health. In other patients a complete reversal in style may occur, adapted to the abrupt change in personality which is sometimes noted with the onset of the mood swing.

B. Comment.—The manic patient is aware of the auditor, as is shown by his comments, directives, and questions. This awareness is sometimes colored by projection of the patient's predominant mood upon the interviewer. The emotion projected does not appear to single out an individual target, but in its diffuseness also includes the auditor. A receptive awareness, in terms of responding or adjusting to the realistic stimulus which the listener presents, is usually lacking. Distractibility, when it occurs, is momentary and fleeting and ordinarily does not appear to redirect the stream of the patient's dominant preoccupations. It would appear as though references to extraneous stimuli served as a convenient stopgap when a topic is exhausted or the patient is at a loss as to the further development of his theme. The carelessness in use of pronouns in reference to antecedents suggests a lack of attentiveness or interest in communication as a guiding motive for his speech. The frequency of particularized references, of naming, of listing, and of itemizing may indicate a need for explicitness. However, an alternative interpretation suggests itself. The emphasis the patient seems to place upon this activity, together with his frequent reference to names of persons and places, to dates, appears to be a confirmation of his own need for certainty. The use of quotations, direct and indirect, is apparently a favored speech mechanism that recurs frequently in these patients. It appears to point to a preoccupation with what other people say and think and suggests a dependence upon the opinion of others.

Expressions of emotion relevant to the immediate or current situation vary with the degree of excitement. They are more frequent in the acutely disturbed patient. In the chronic, less excited, but loquacious patient the impression is that of lack of emotional tone and coloring rather than of richness of emotional expression.

The unconscious selection of idioms, stereotyped or conventional phrases, reflects characteristics of individual personality traits rather than of manic speech as a whole. But the excessive use of these speech mechanizations, as seen in individual patients, is rather striking. In these patients the mechanical pattern becomes so fixed and ubiquitous as to dominate the entire language pattern. It adds to the impression of monotony that is already presented by the repetitious and redundant use of words and phrases.

Some, although not all, of these features have been noted in each of the 10 patients during their manic mood swing. Whatever speech mechanization presents itself emphatically in the individual patient, whether it is the use of quotations, of stereotyped expressions, or any other form, the recurrence is so decided as to detract from the flexibility of the language. Vividness and emphasis are present in some manic language patterns. A sense of liveliness, movement, and spontaneity is not characteristic of the individual style.

II. Syntactics

A. *Observations.*—1. Grammatical Structure: The grammatical structure of spoken language varies over a wide range, from short, precise, formally intact sentences, to a loose, disjointed, rambling style, to fragmentations consisting of words and phrases. "And I was an only child. You don't want my medical history. I had rickets as a child. I was a puny child." "The man's wife, the one I ran away with, I said, well, don't think about it now, dear." ". . . rip the lip and spit on no one . . . out, out, black spot . . . freckle, freckle, amen, amen . . . Jesus Christ, hail Mary, full of grace, grapes, gripes . . . still enough words for the birds." To a large extent the degree of disorganization of language parallels the phase of excitement of the patient and the chronicity of the illness. The last is more typical of the acutely disturbed patient; the second, of a long-continued active hypomanic state; the first, of a relatively intact patient with periodic mood swings. In a state of manic excitement, expletives, words connected by sound associations, phrases, rather than sentences, form the burden of the verbal output. Patients with chronic hypomanic reactions of many years' duration often retain a remarkable loquacity quite independent of an auditor. The production of these patients are apt to be long involved strings of words and phrases, thrown together with connectives, and with grammatical form ignored.

2. Tense: Verb tense seems to be largely in the past (with the exception of the acutely disturbed patient), to some extent in the present, rarely in the future. This is correlated with the preponderantly anecdotal content. Unfortunately, the expansive grandiose type of manic-reaction type was not available for this study, and here projection into the future might be apparent.

3. Negation: The use of negatives—no, never, none—was not excessive, although two patients used them for emphasis. The production of all these patients was carefully scrutinized for the appearance of negation on the hypothesis that denial or protest might manifest itself particularly in this type of language behavior.

4. Logical Consistency: It is rather difficult to place one's finger on the precise defect in the logic of manic speech. Individual sentences are often formally correct; words are related to each other in proper logical sequences. The same holds true of the relationship of sentence to sentence when the laws of association are clear or reasonably transparent to the auditor. When one takes into consideration the context of a segment of speech related to a given topic, it becomes apparent that, although much is said about and around this topic, development and progression toward a specific goal are lacking. Intent and purposiveness, which ordinarily structure what is said into a meaningful whole, are lacking.

The method by which this inconsistency is achieved appears to be largely on the basis of the logical connectives and the associations introduced. Logical words (and,

if, but, then, because, etc.), which lend logical continuity to a sentence, are frequently found to link unrelated elements. "I have never been to Prussia, *but* they are very rude"; "I went to Radcliffe and took graduate work in 1916 *and* I had a suspension for sterility"; "They never show the slightest temper; *therefore* the child grows up with a nurse."

5. Associations: Associations need not be more numerous or more richly elaborate than ordinarily occur. What one observes, actually, is a defect in selectivity and what appears to be a compulsive need to make explicit verbally the associations which cluster around a topic. The critical and discriminating faculty, which ordinarily ignores the irrelevant and selects specifically those associations which produce a forward movement toward the guiding idea, is not utilized.

The associative transition between sentences is often of a simple nature and seems to follow discernible laws. Sound associations are well recognized. Often the key word or phrase in a sentence is carried over and used again in the next. "I am perfectly *happy*. I can be *happy* wherever I am. I could be deprived of everything and still be *happy*"; and "*Young* people always spend all the income they make. I get along better with the *young*. I love the *young*." Examples such as these are frequent and give an impression of repetitions and redundancy. Associations made by assigning the individual to a class are also noted: "My friend *Serge*, whom I adored. The *Russians* are very spiritual, not at all sensual." Associations on the basis of contiguity or continuity in time or place are also frequently noted. "I would like to follow through in the afternoon with some badminton, possibly a little bowling, maybe billiards, uh, I've never played these games *since I left here*. Mr. M. is capable of directing me. He successfully did that *when I was here before*." (Incidentally this patient was an exception in freely employing tentative phrases, such as "possibly," "maybe," "a little." His insecurity, so well disguised by a pompous and positive approach in many areas, slipped out in this felicitous choice of words.) Another patient, in discussing plans for the future, switched back to recent past history: "I think if I enroll myself as a special student to get into the school of library service I would find the courses more interesting. I had experience in M. library in the last three years. I graduated from W. in June of '49. I taught at L. Academy." Another patient exhibited a strong thread in her associations by comparison and contrast in time: "I'm having a delightful time here on C. Much *nicer* than *last time*. *Last time* I was *too sick* to enjoy my sojourn here; *this time* I feel ever so much *better*. *Today* I think I'm turning yellow. *Every day* I think my skin takes on a new shade. *After I left* this place, *I felt very well*. When *I was here last summer*, I had *no pain whatever*." Again, it is to be noted that when one traces the qualities of the associations that an individual patient uses, a characteristic pattern often stands out. Associations are seen to be predominantly of one or two patterns, verbal, by contiguity, contrast, etc., without the flexibility of changing easily among the many possible pathways. In one hostile, slightly paranoid manic patient associations seemed to be carried along, determined chiefly by the undercurrent of her suspicious and angry feelings. "They tell me hardly anything about one that anybody in their life felt they don't know about it. Well, we have all our books and records and so forth. You know that I know what's been going on, and I've been checking up, and I haven't even bothered to discuss what has been perfectly apparent for some time. But let's start from here now without a stew. I think the doctor isn't very anxious to understand that."

B. Comment.—Disorganization of the manic language pattern in terms of its conventional grammatical structure appears to be a factor correlated with the intensity and chronicity of illness rather than with its specific nature. However, some defect in the logical development of theme is noted even when formal linguistic structure is relatively intact. A single sentence, or even group of connected sentences, lifted from an interview may be quite correct, logical, and informative. A defect in meaning is, however, recognized when one views a larger segment of the speech pattern, or the interview as a whole. One becomes aware of a deficit, rather than a distortion of meaning. There appears to be an absence of a preconceived pattern or goal, which lends purposiveness and direction to ordinary speech. Instead, one finds a kind of cumulative, additive effect. Bits of information and observation are introduced, all of them related to the topic or theme in some way, but not all of them together related in a single, organized way. Sometimes the use of logical words as connectives seems incongruous; sometimes the associations introduced, although legitimately related to the topic or idea, are not in line with a consistently apparent aspect of the topic. The manic patient's associations, though often irrelevant to a consistent purpose, usually are relevant to the specific topic. The laws of association which appear to function are often superficial clang or verbal associations, associations in terms of time or place or members of a class, or based on prevailing feeling. They may be fairly transparent to the listener who knows the patient. There is far less evidence of associations based on complex introspective individual meaning.

III. Semantics

A. Observations.—The content analysis of the spontaneous productions of patients during a manic phase shows certain consistent trends which stand out in the group as a whole. It is true that they are modified in individual patients, dependent upon the underlying personality and character structure. The outstanding features which emerge when one is looking for similarities, rather than individual differences, are as follows:

1. Content: In the main, the subject matter has to do with things or events, rather than with the meaning of things or events. It is concerned with people, events, circumstances, occurrences that have existence external to the patient, things that one ordinarily speaks of as factual, or "objective reality." Within this area a further recurrence is noted. Many of the patients are primarily concerned specifically with people, how they behaved, what they did or said, and most specifically with anecdotes or accounts of their own interaction and relationship with people and events in the past. One would conjecture from this that people who stand in specific relationship to the patient, such as family and relatives, would be involved. This is borne out in fact, as well as theory. References to parents, siblings, husband or wife, and others in the family constellation are frequent.

2. Theme: Despite the observation previously made that a purposiveness, or goal direction, is not evident, a predominant theme or themes stand out by repetition. One may not always know what the patient is trying to say, but what he is talking about is readily perceived. For example, the theme of preoccupation of one patient was his dependent and competitive relationship to a family of effective, dynamic older brothers. In another case, that of an 18-year-old youth, it was that of his own status with his contemporaries and how he compared with his successful

father. A distressed nun was preoccupied with the value she was given by the superiors in her community. A young medical secretary of humble family background questioned her acceptance as an intellectual equal by her associates. These are examples of theme emerging from verbal content. Of course, the theme is not stated in so many words. The patient gives anecdote after anecdote, depicts situation after situation illustrative of his general problem. Not infrequently a key statement can be picked out in which the patient's conflict appears objectified. The young secretary who leaned so heavily upon demonstrating her intellectual approach to problems, whose one fixed method of dealing with emotional dependent needs was to make an intellectual rationalization, who prefaced the majority of her statements with "I think," said: "I think psychiatric treatment is wonderful. In any disease, even if you have a backache or a sore foot. People don't realize how thinking dominates the emotions . . . . I think you should get a doctor who is a friend."

3. Self-Evaluation: When one examines the nature of the relatedness of speaker to content, another kind of thematic quality emerges which is of such frequent incidence as to impress one. This is the quality of comparing, evaluating, measuring himself against the other person or persons. This is done in a characteristic way. Many statements are introduced of what other people have said or say about the patient, or events are described which seem to indicate how others feel toward him. Many self-observations of an idealized sort are made that indicate very clearly the kind of person the patient would like to be. An idealized self-image often emerges very strongly. This often occurs together with emphatic denial and rejection of those qualities which on the basis of the history and observation of the patient one would most strongly suspect as being present. The boy, referred to previously, who, harassed and driven by a tremendous need to stand well with his contemporaries, had extended himself into so many activities that he literally did not have a free moment, said: "I never, never, never sense that I am being rushed into anything."

Mechanisms of denial and of overcompensation are so frequently woven into the texture of the language activities that the entire content of an interview has a strong flavor of reaction formation.

Self-observation and evaluation, direct or as reflected in the comments of others; concern with critical observation of other people and their activities, judgments, evaluations, and comparisons, are themes very much in the foreground. The patient seems to evaluate his relationship to the world in one predominant manner, that of the critic and observer, somewhat as participant, but very little as a sensient, experiencing subject. If one uses William James's happy dichotomy of the observing "I" and the experiencing "me," the weight of the patient's own estimation of his self-image seems to be preeminently the former. It is of interest that the quality of verbs used in conjunction with the pronoun "I" are often "I think," "I know," and others in the same order of cognitive approach. It suggests a strong tendency toward a rational perspective. The very fact that so often statements are preceded by an introductory "I think" or "I know," rather than a direct presentation of the material, further suggests a tendency to isolate oneself, or, at least, to draw a distinction between the commentator and what is commented upon. A sharp line between subject and object seems to be maintained.

4. Insight into Illness: The patient's illness is a subject very frequently introduced spontaneously. There appears to be sufficient critical faculty to differentiate

the present state of affairs from past experiences. This awareness is present but may be treated quite differently by different patients. One patient insisted repeatedly: "I am well, I am happy, I am not sick"; another expansive, elated patient referred to "being practically back to normal." Another plainly said, "I am high." These observations, made through denial, minimizing, or acceptance, were generally in line with the individual characteristic defense mechanisms.

5. Vocabulary: Vocabulary and word choice are, again, more highly correlated with the individual than with the syndrome of illness. Yet general trends are noted. Similes and metaphorical expressions are ordinarily not prominent. The conventional and prosaic seems to outweigh the imaginative. The question of precision versus vagueness is a complex one. The impression one receives from a total interview is often so vague that it would be difficult to reformulate what the patient has said. But many quite specific facts that he has stated come readily to mind. A tentative formulation that would embrace both observations might be that the patient uses specificity in details as a last resort of defense, and clings to names, dates, etc., as a protection against the threat of complete disorganization of his thinking.

B. Comment.—The language pattern of the manic patient bears a distinct stamp. It is representational, rather than presentational; if one may draw an analogy to art, it has the quality of productions which depict, mirror, or reflect the world as it is perceived, rather than the quality of those in which the medium of art seems to convey directly the subjective experience of the artist. Language of manic patients would seem more akin to the former. This generalization is better correlated with the language of those patients who are designated as manic-depressive. When schizoid personality traits underlie the mood swing, the subjective quality emerges more strongly.

Another distinguishing feature, also subject to the same modification, would seem to be that language behavior of manic patients shows differentiation and rather sharp division between the subject and the world external to the subject. However distorted and colored by affect or by misinterpretation in the area of value and judgment, there is little evidence of fusion of what is perceived with the person perceiving. In a curious way, the same thing seems to hold true in terms of the patient's relationship to the introspective world. Manic language gives little evidence of a fusion with fantasy or symbolism.

SUMMARY

The more outstanding characteristics of language patterns during a manic reaction in this group of 10 patients appear as follows:

The language does not appear primarily designed to meet the requirements of communication. Mechanizations, such as personal idioms and conventional phrases, detract from flexibility of expression. The use of proper names and of quotations is prominent, as are words of exaggeration and emphasis. The style is redundant and monotonous and most frequently shades toward the prosaic and conventional. Ideation lacks forward movement and goal direction. Associations are most frequently selected by superficial and discernible laws or are conditioned by affect. Symbolic values or introspective meaning does not seem to influence their direction. Content is heavily thematic, and centers about people, events in the past, and self-evaluation. The patient appears to play the role of observer with a predominantly rational approach to the objective world.

COMMENT

The pattern of any language appears incomplete unless one has some idea of the purpose for which it is used and the role it plays. Reference has been made by Lewin [5] to the manic patient's flight into the superficial and the verbal. He characterizes the speech of these patients as used primarily to distract and to conceal. English [6] described the manic as aggressively blurting out all the things he has been afraid to express. Such a divergence of views probably arises in part from the stage of the manic disorder under scrutiny and in part from the different functions which speech may serve. The increased talkativeness and pressure of speech which distinguish all phases of the manic reaction may be viewed as a part of the general increase in motor activity (as such it may represent a discharge of tension, an attempt to master anxiety, a substitute for action, etc.). But as a part of general behavior language seems to have purpose and function of its own lying within just that area where it appears least effective, namely, communication. It may appear as an attempt on the patient's part to secure relatedness to the human environment, an attempt that is rendered ineffective by the interplay of the same limitations that hamper the manic patient in his general adjustment to interpersonal relationships. He seems to have one predominant mode of adaptation—impressing himself on his human environment takes precedence over receptivity and responsiveness to this environment. In his language behavior the same one-sided intent is manifested. Perhaps this is a distortion of what may be the patient's habitual way of using language as a manipulative or evocative tool to structure a situation.

The lack of flexibility and the rigidity of language pattern described here may not be unique to the manic patient. It is possible that language may exhibit traits and bring into focus essential features of rigidity and unadaptability common to both neuroses and psychoses. The concept of "obligatory repetition," formulated by Kubie [7] in his discussion of neurotic potential and adaptation, characterizes behavior determined by unconscious forces as "rigid, repetitive, unadaptive, ineffectual compromise." In manic patients perseveration of theme, repetitiveness in the use of habitual conventions and stock phrases, the endless paraphrasing of relatively few observations and ideas, the pseudorational approach to these ideas, align themselves into a meaningful pattern. This pattern may be indicative of the manic patient's general reactive tendencies manifested at other levels of behavior.

Defense processes that stand in the foreground during a manic reaction have been described by Lewin [8] and Deutsch [9] as characteristically those of denial, repudiation, and disavowal. In the language pattern the predominance of words of exaggeration and emphasis, of words denoting certainty, the lack of fine discrimination, often reinforce this clinical impression. One would be tempted to add overcompensation and reaction formation to the mechanisms of defense, on the basis of

5. Lewin, B.: Comments on Hypomanic and Related States, Psychoanalyt. Rev. **28**:86-91, 1941.

6. English, O. S.: Observation of Trends in Manic-Depressive Psychoses, Psychiatry **12**:125-134, 1949.

7. Kubie, L. S.: The Neurotic Potential and Human Adaptation, in Adaptation, Edited by John Romano, Ithaca, N. Y., Cornell University Press, 1949, pp. 77-96.

8. Lewin, B.: Psychoanalysis of Elation, New York, W. W. Norton & Company, Inc., 1950.

9. Deutsch, H.: Psychology of Manic-Depressive States, Internat. J. Psycho-Analysis **14**:149-151, 1933.

scrutiny of the kind of self-observations frequently made by the patient and of his selection of quotations of the comments others have made about him. The "self-image" in the manic patient seems to have a special quality of emerging as reflected back to the patient from the external environment, or as perceived objectively by a process whereby the patient stands off and observes himself. Dooley [10] has referred to a "living in two persons," actor and observer, as a concomitant of manic-depressive states. In the language pattern such a cleavage can sometimes be traced, objectified in the frequent intrusion of "I think" and "I believe," and in the preponderance of biographical and anecdotal material. Fromm-Reichmann [4] has found a high incidence of similarity in family constellations, the role of the patient within the family orbit, and the pressures and conflicts sustained by the patient within this orbit. In the emergence of themes during the manic phase, there is a parallel in the high incidence of preoccupation with family and relationships within the family.

Certain formulations, such as "flight of ideas," "flight into reality," "throwing off the yoke of the superego," have become identified with manic disorder. Study of the language of these patients suggests that a reexamination in the light of language pattern may introduce some modifications of these concepts. Ideation seems limited in content, rather than increased, if one is to judge by repetition and recurrence of theme. What on the surface suggests a wealth of association, on closer inspection raises the question whether these associations reflect much movement in thought. They seem so often to be attributes inherent in the topic itself and do not lead away from it, except superficially. Stockert [2] presented the interesting point of view that "association is really slowed down and loosened . . . the total concept is lost . . . the empty void filled in by seizing upon associations brought up by sensory phenomena." One would question whether ideas are characterized by "flight" or increase. The associations may well be the same as or fewer than those which ordinarily occur, but made explicit either by a compulsive need to express them or because of failure to select those pertinent to the goal. The patient is most emphatically occupied with reality. The point at issue is whether this represents a "flight into . . ." or is a continuum of the usual state of events for the patient. Fromm-Reichmann [4] stated that the reports given during manic episodes are stereotypically identical with those given by the patient when depressed. Language behavior with regard to evidence for "throwing off the yoke of the superego" shows an interesting, and perhaps progressive, change. In the violently disturbed patient the concept may hold. But in the manic reaction which does not proceed to this severity, language shows evidence of superego function. Masserman [11] expressed the opinion that the superego is as harsh and relentless as ever. The demonstration of an active, idealized self-image would seem to indicate this. Evidence of strong defense mechanisms (exaggeration, denial as exemplified in language) operating within the economy of the individual personality implies the presence of superego demands.

Language pattern, with respect to variations in the individual patient and with respect to similarities that hold for the manic state, provides corroborative evidence of dynamic formulations and provides source material that psychiatry is just beginning to explore.

10. Dooley, L.: Relation of Humor to Masochism, Psychoanalyt. Rev. **28**:37-45, 1941.

11. Masserman, J. H.: Psychodynamics in Manic-Depressive Psychoses, Psychoanalyt. Rev. **28**:466-478, 1941.

INCISURAL SCLEROSIS AND TEMPORAL LOBE SEIZURES PRODUCED BY HIPPOCAMPAL HERNIATION AT BIRTH

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DURING recent years it has become increasingly evident that patients with temporal lobe seizures constitute one of the largest groups among those who have epileptic attacks. The origin of epileptogenic discharge in various parts of the temporal cortex produces a variety of initiating seizure phenomena, such as abdominal aura, cephalic aura, olfactory aura, psychical hallucinations (or dream states), illusions of perception (e. g., déjà vu phenomena), and automatism.

In a series of 157 cases of seizures originating in the temporal lobe, we have analyzed the anatomical location and pathology of the abnormalities which were found on surgical exploration and cortical excision. In 100 of these cases (approximately 63%) the pathological findings suggested that compression or anoxia during birth or infancy was the cause. It is this group of cases that we wish to discuss particularly. In the remaining 57 cases we found evidence of postnatal injury, intracranial infection, or neoplasm in the temporal region.

Temporal lobe seizures may begin in childhood and continue into adult life, or the onset may be delayed until the second or third decade although the cause is oftenest to be found in the mechanism of birth compression. The operative technique which is employed in the treatment of these patients is described in a separate paper by Penfield and Baldwin,[1] and a follow-up study of the results of surgical therapy for temporal lobe seizures was reported by Penfield and Flanigin.[2]

CLINICAL INVESTIGATION

No patient in this series was subjected to operation unless the preoperative study led to the conclusion that the epileptogenic focus was situated in one temporal

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1. Penfield, W., and Baldwin, M.: Temporal Lobe Seizures and the Technique of Surgical Therapy, Ann. Surg. **136**:625-634 (Oct.) 1952.

2. Penfield, W., and Flanigin, H.: Surgical Therapy of Temporal Lobe Seizures, Arch. Neurol. & Psychiat. **64**:491-500 (Oct.) 1950.

lobe. In many cases simple x-ray films showed asymmetry of the skull, with relative smallness of the temporal fossa and elevation of the petrous ridge on the side of the atrophic temporal lobe. When such smallness existed, it was taken as evidence that the atrophy had been produced within the first two years of life, probably at the time of birth. Pneumoencephalograms often demonstrated slight comparative enlargement of the temporal horn of the lateral ventricle on the atrophic side.

In most cases the preoperative electroencephalogram indicated an origin of abnormal potentials in the temporal lobe which was to be exposed at operation. In occasional cases, the electroencephalographic abnormalities seemed to be bitemporal, but the pattern of seizure onset made it obvious that the focus must be deep in one temporal region. Operation was not undertaken when the electroencephalographic discharge was clearly originating in subcortical centers or when there seemed to be a focus in each temporal region.

The anatomical evidence has led us to rule out congenital abnormality as the cause. This point of view is substantiated by the fact that five patients in the series were twins. At least two of these twin pairs were identical. Four of the companion twins developed normally, without seizures, and the fifth died at birth.

Electrocorticograms taken at the time of operation usually showed the major electrical abnormality to be present on or near the area of gross abnormality. In many cases electrical stimulation in these areas reproduced the initial phenomenon or warning aura of the patient's attacks.

PATHOLOGICAL FINDINGS

Gross and microscopic abnormalities were found in all these cases. The gross lesions varied from atrophy or toughness of a single gyrus to atrophy of the entire temporal lobe and parts of adjacent cortex. The gyri were often shrunken, yellow, avascular, and obviously smaller than normal.

The commonest abnormality consisted of sclerotic areas of cortex in the inferior and medial part of the temporal lobe. The uncus, hippocampal gyrus, and part of the first temporal gyrus were usually involved (Fig. 1). We shall demonstrate that this type of abnormality could have been produced by compression of the head and herniation of the hippocampal regions through the incisura of the tentorium at birth, and we have called this entity incisural sclerosis.

Histological study of the excised areas usually revealed an increase in fibrous astrocytes in the gray and white matter. The overlying pia was often thickened, with intimal or adventitial thickening of the pial vessels. In some cases there were focal losses of neurones and nerve fibers, with cystic degeneration in a few cases. In others, the loss of neurones was not apparent, but fibrous astrocytes were increased in the gray matter. In some cases these changes were minimal; in others the gliosis was so marked that the surgical specimens resembled astrocytomas or hamartomas.

Two cases may be cited to illustrate the pathological findings.

CASE 1.—G. F., a 45-year-old housewife, had no history of natal or postnatal injury or severe infection. Seizures began when she was 37 years of age. In each attack she had an initial feeling of fear and a perceptual illusion that things were far away from her. An electrocorticographic abnormality was found in the first temporal gyrus anteriorly. This gyrus was obviously narrow.

During removal it seemed tough, avascular, and yellowish. The abnormality extended into the uncus and hippocampal gyrus.

The pathological change was most obvious in the gray matter, but the underlying white matter was abnormal as well. The overlying pia was milky white, and the pial vessels appeared thickened. Histologically, there was a diffuse increase in fibrous astrocytes in the gray and white matter (Fig. 2*A*, *B*, *C*). Abnormally large and binucleate astrocytes were seen. Neurones and fibers were lost in small focal areas.

CASE 2.—P. S., a man aged 26, had onset of attacks at the age of 12. There was a history of a difficult, instrumental birth. On x-ray examination, the right half of the skull appeared slightly smaller than the left, and the petrous ridge was elevated on the right side. His seizures were characterized by a psychical hallucination, a cephalic aura, and automatism, accompanied by movements of mastication. Electroencephalograms indicated that the seizures originated in the right temporal lobe.

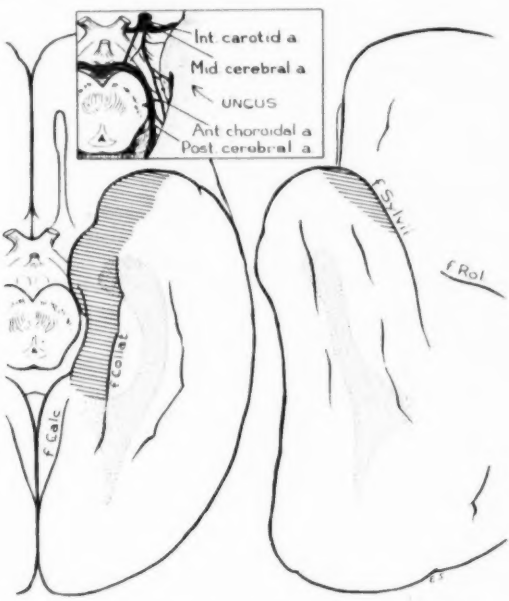

Fig. 1.—Incisural sclerosis. The hatched area is the most frequent site of sclerosis produced by temporary herniation of the temporal lobe through the incisura of the tentorium at the time of birth. The arteries supplying this region are shown in the inset.

At operation adhesions were noted between the dura and the arachnoid. The pia was thickened and white over the Sylvian fissure anteriorly. There were marked atrophy, toughness, and avascularity of the first temporal convolution, and this abnormality extended into the uncus and hippocampal gyrus. Close to the tip of the inferior horn the tissue was gelatinoid, gray, and tough.

Histologically, this gelatinoid tissue contained numerous fibrous astrocytes and some giant astrocytes. The uncus and hippocampus showed pronounced increase in fibrous astrocytes (Fig. 2*D*, *E*, *F*).

Sometimes the history suggested the actual cause. In Case 2, the history, the roentgenograms, and operative and pathological findings all pointed to birth compression as the cause. In many cases, however, as in Case 1, the history gave no

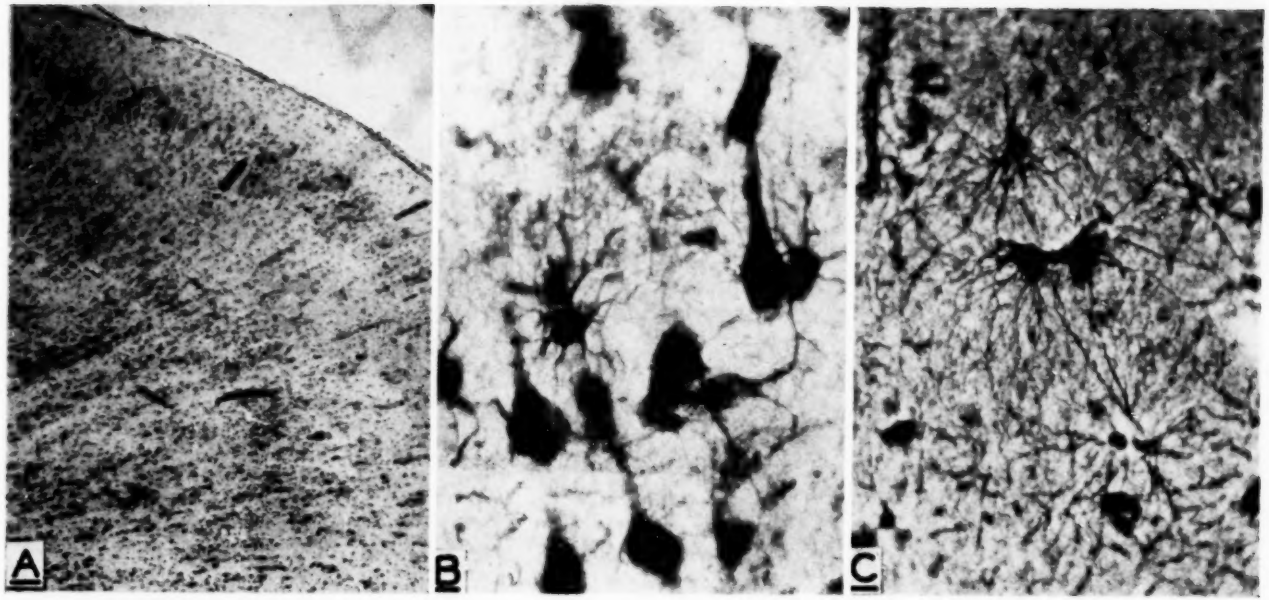

Fig. 2.—Photomicrographs in cases of temporal lobe seizures believed to be due to hippocampal herniation and the resulting ischemia at birth. *A*, focal loss of neurones; *B*, increase in fibrous astrocytes in the gray matter; *C*, abnormal binucleate astrocytes.

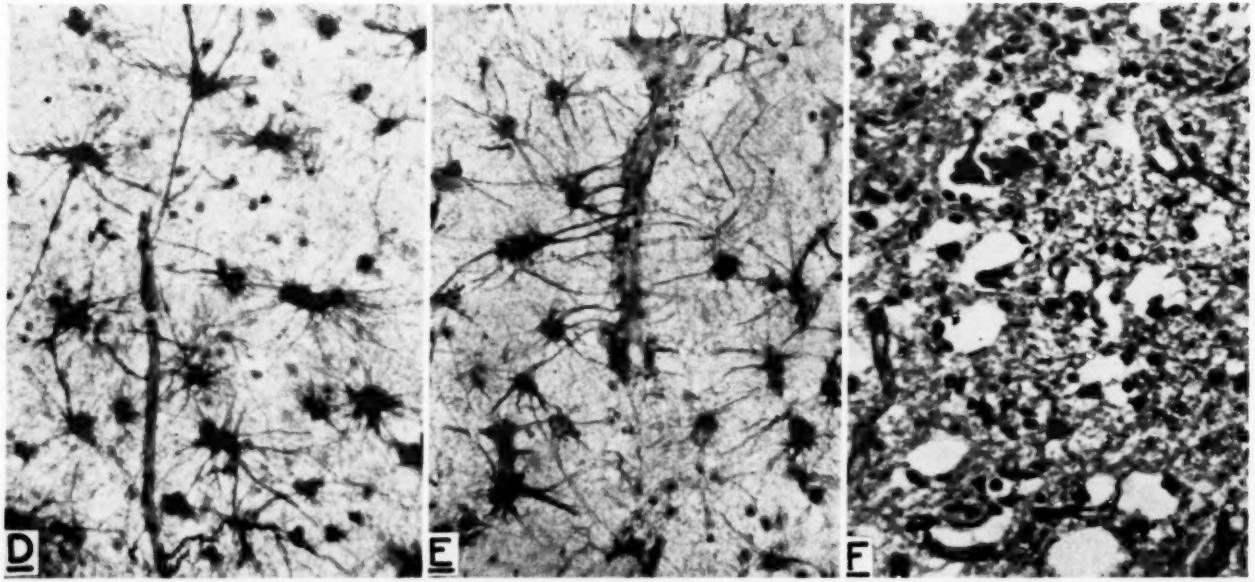

Fig. 2 (cont.).—*D* and *E*, increase in fibrous astrocytes in the gray and white matter, respectively; *F*, cystic degeneration and gliosis.

clue to the etiology; in fact, it was often misleading, as demonstrated by the eventual outcome of operation. The accompanying Table illustrates these facts.

In Group 2, with a history of postnatal head injury, only 29 of the 49 patients had pathological findings consistent with the history. In Group 3, with a history of infection at or near the time of onset of seizures, only 11 of 26 patients had pathological findings consistent with the history. The other patients in these two groups had pathological findings resembling the group with a definite history of birth injury, better called birth-compression anoxia. In the three cases originally classified as instances of hamartomas, the tissue might well be reclassified as a form of unusual sclerotic reaction to ischemia at birth. Practically all the group with no significant or related history showed pathological findings similar to the birth-injury group.

Etiologic Factors Suggested by Clinical History

Group			No. of Cases
1	History of difficult birth		25
2	History of postnatal head injury		49
	(*a*) Minor injury without loss of consciousness	9	
	(*b*) Uncertain severity	15	
	(*c*) Major injury	25	
3	History of possibly related infections		26
	(*a*) Brain abscess	4	
	(*b*) "Encephalitis"	2	
	(*c*) Meningitis	5	
	(*d*) First attack during a febrile illness of various types (influenza, measles, pertussis)	11	
	(*e*) Febrile illness with attacks several weeks afterward	4	
4	History or other evidence suggesting neoplasm		18
	Pathological findings in this group:		
	(*a*) Hemangioma	3	
	(*b*) Astrocytoma	8	
	(*c*) Cholesteatoma	2	
	(*d*) Glioma, unclassified	2	
	(*e*) Hamartoma (probably result of natal ischemia)	3	
5	History of severe anoxia during general anesthesia		2
6	History of seizures following injection of pertussis toxoid		2
7	No related history		35
	Total		157

When the cases in all these groups were reviewed from the standpoint of the history, physical examination, and x-ray, electroencephalographic, and pathological findings, it became apparent that in approximately 100 of the 157 cases the abnormality could have been caused by anoxia or injury during birth or infancy.

In some of these cases the history clearly indicated a prolonged and difficult labor, but in other cases labor was not considered difficult and there was no history of injury or obvious deformity at birth. In only one case was there a history of maternal illness (mild preeclampsia) that might have affected the fetus.

In consideration of this material, certain questions present themselves. Why should the temporal lobe be so susceptible to injury at or near the time of birth even when there was no suspicion of trouble until the onset of seizures, many years later? Why should the undersurface of the temporal lobe, especially the uncus and hippocampal gyrus, be so frequently involved? If the damage were due to an external violence, why should the instances of injury to the lateral surfaces of the brain be so rare?

In the consideration of these questions, we have reviewed the embryology and blood supply of the temporal lobe and considered the mechanics of head compression at the time of birth, in the hope of discovering the cause of temporal lobe epilepsy.

EMBRYOLOGICAL ASPECTS

When the human embryo has reached the age of 18 weeks (C-R length, 160 mm.), the cortex is growing faster than the insula and is forming folds which will

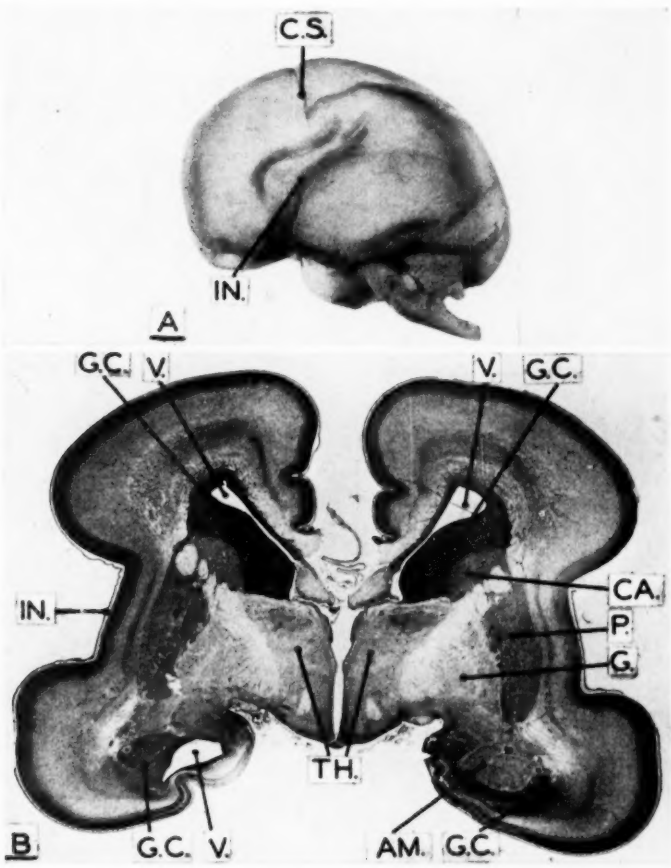

Fig. 3.—*A*, photograph of the brain of an 18-week fetus (C-R length, 160 mm.). *C. S.* is central sulcus; *IN.*, insula. *B*, cross section of the brain in *A*; cresyl violet stain. *V.*, is ventricle; *G. C.*, germinal center; *IN.*, insula; *TH.*, thalamus; *AM.*, amygdaloid nucleus; *CA.*, caudate nucleus; *P.*, putamen; *G.*, globus pallidus.

gradually conceal it from view (Fig. 3). Cross section at this stage shows that the germinal centers (sometimes called germinal matrix, or *Mutterschicht*) are still large and active around the lateral ventricles. The cortex is developing rudimentary layers, but there remain numerous neuroblasts migrating through the intermediate zone.

At birth the insula is almost hidden from view by approximation of the opercula (Fig. 4). The fissure formed by this approximation is called the lateral fissure, or fissure of Sylvius. The frontal operculum is the last to approximate the others, and the anterior part of the fissure may be slightly open at birth. The cortex has become differentiated into layers at birth, but the neurones have not fully matured. This immaturity can be seen by comparing the neurones of the cornu ammonis of a newborn child with those of an adult at the same magnification (Fig. 5*C* and *D*).

The germinal centers about the lateral ventricles are still active at birth but have become smaller (Fig. 5*A* and *B*). Ischemia or injury to the brain at this age may therefore affect the brain differently than it would at a later period, when development and maturation are completed. Nielson and Courville,[3] Courville,[4] Penfield

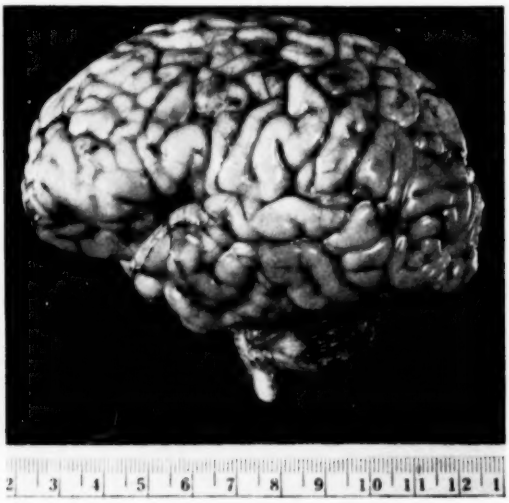

Fig. 4.—Photograph of the brain of a full-term newborn infant. Lateral view showing the normal development of gyri and sulci at birth. The fissure of Sylvius is not yet completely closed.

and Keith,[5] and Penfield and Humphreys [6] have emphasized the role of birth injury and asphyxia in epilepsy. As Ford [7] pointed out, however, there does not seem to be any general agreement among neurophathologists about the late results of cerebral birth injury. The lesions we have studied may be the late results of anoxia or injury. The patients varied in age from 3 to 54 years at the time of operation.

3. Nielson, J. M., and Courville, C. B.: Role of Birth Injury and Asphyxia in Idiopathic Epilepsy, Neurology **1**:48-52 (Jan.-Feb.) 1951.

4. Courville, C. B.: Contributions to the Study of Cerebral Anoxia, Bull. Los Angeles Neurol. Soc. **15**:99-195 (Sept.) 1950.

5. Penfield, W., and Keith, H. M.: Focal Epileptogenic Lesions of Birth and Infancy, with Report of 8 Cases, Am. J. Dis. Child. **59**:718-738 (April) 1940.

6. Penfield, W., and Humphreys, S.: Epileptogenic Lesions of the Brain: Histologic Study, Arch. Neurol. & Psychiat. **43**:240-261 (Feb.) 1940.

7. Ford, F. R.: Cerebral Birth Injuries and Their Results, Medicine **5**:121-194 (May) 1926.

The large increase in the size of the brain after birth is due primarily to the formation of myelin, rather than an increase in the size or numbers of ganglion cell bodies. With a few exceptions, myelination may be said to begin about the time of birth and to continue for several years.

Thus, to summarize the first point, the brain of the newborn is far from being fully developed. The neurones have not fully matured. Myelination is just beginning its major increase. The germinal centers are still present. Asphyxia or birth injury may alter the normal development and growth of the part affected.

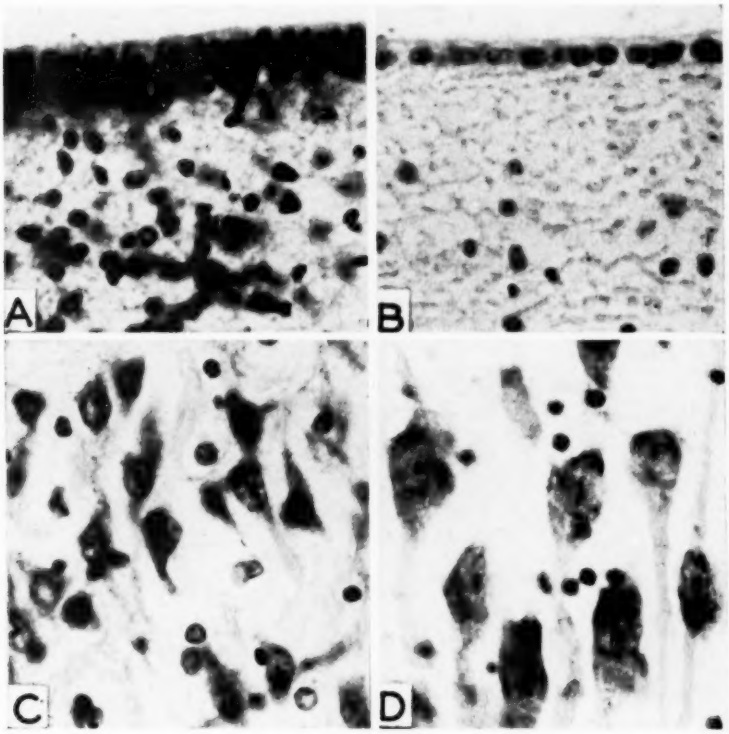

Fig. 5.—*A*, ependymal lining and germinal center of a full-term newborn infant; *B*, ependymal lining of an adult; *C*, neurones of the cornu ammonis of a full-term newborn infant; *D*, neurones of the cornu ammonis of an adult. Cresyl violet stain; × 100.

CIRCULATORY ASPECTS

Spielmeyer [8] recognized the fact that ganglion cells may be lost and glial proliferation found in the cornu ammonis in epilepsy. He would go no further, however, than state that organic occlusion of the circulation produces changes like those seen in epilepsy, and in similar locations. He concluded, "in epilepsy, also, an impediment to the circulation must have been present, and since organic impedi-

8. Spielmeyer, W.: Anatomic Substratum of the Convulsive State, Arch. Neurol. & Psychiat. **23**:869-875 (May) 1930.

ments are absent, the circulatory function must at some time have been disturbed." He further concluded that in partial hindrances to the blood supply it was those parts with the poorest supply which suffered first, whereas in other parts of the brain, with a better blood supply, a compensatory reaction was possible.

The temporal lobe is supplied by three arteries: the middle cerebral, the posterior cerebral, and the anterior choroidal. The middle cerebral artery supplies the temporal pole, and the superior and middle temporal gyri. The posterior cerebral artery supplies the hippocampal gyrus (except for the uncus, which is supplied by

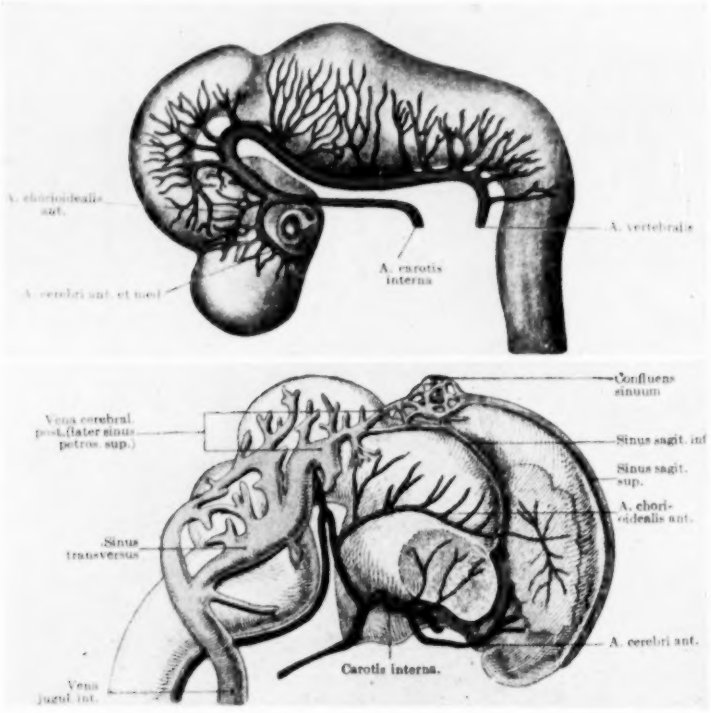

Fig. 6.—Graphic reconstruction of the vessels of the brain in a 9-mm. (above) and a 38-mm. (below) human embryo. From Kiebel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, Vol. 2, p. 623; reprinted by permission of the publishers.

the choroidal artery) and the inferior temporal and fusiform gyri. The anterior choroidal artery has certain peculiarities and will be discussed in detail.

In the 9-mm. embryo (age about 5 weeks) the internal carotid artery splits into two terminal trunks: a small anterior and a large posterior trunk. The latter continues into the basilar artery. The anterior trunk gives off the anterior choroidal artery (Fig. 6), which is prominent at this age, and crosses the side of the forebrain, encircling the optic cup above. The anterior trunk becomes the anterior cerebral artery and gives off many branches to the cerebral vesicle, which later

fuse to become a single trunk, the middle cerebral artery (Kiebel and Mall [9]). The posterior terminal trunk of the carotid artery gives off many branches to the sides of the midbrain, and these are represented later by a single trunk, the posterior cerebral artery.

In the 38-mm. embryo (age about 9 weeks) the anterior choroidal artery continues as a prominent vessel (Fig. 6) but in later stages becomes comparatively small, while the middle and posterior cerebral arteries enlarge (Kiebel and Mall [9]).

In the adult, the anterior choroidal artery sends branches to the uncus, cornu ammonis, amygdala, globus pallidus, anterior commissure, parts of the caudate nucleus, optic tract, fascia dentata, lateral geniculate body, posterior two-thirds of the internal capsule, middle third of the cerebral peduncle, and sometimes the substantia nigra and ventral nuclei of the thalamus (Abbie [10]; Alexander [11]). Variations are frequent, however, and some of these areas have additional arterial supply from other vessels. Anastomoses with branches of the posterior cerebral artery are frequent.

At the time of birth, the anterior choroidal artery and branches of the middle cerebral artery and posterior cerebral artery seem particularly vulnerable to shift of the brain and herniation of the hippocampal regions. The anterior choroidal artery is comparatively large in the newborn (Fig. 7), and it seems to supply a larger area at this stage than it does in the adult (Fig. 8). Also, the branches of the middle cerebral artery to the superior surface of the temporal lobe and the branches of the posterior cerebral artery to the inferior surface of the temporal lobe are relatively large, and perhaps more vulnerable to hippocampal herniation in the newborn (Fig. 7). These differences in comparative size and distribution in the newborn may account for the abnormalities found in the epileptic patients described previously.

When seen in adult life, these abnormalities appear to be in the distribution of branches of all three of these arteries, but hippocampal herniation in the adult brain seldom involves the branches of the middle cerebral artery. Compression of the posterior cerebral artery and its branches due to hippocampal herniation is often seen in the adult brain in cases of brain tumor, intracerebral hemorrhage, and cerebral edema. Because of its small size in the adult, compression of the anterior choroidal artery is less apparent in the adult brain in hippocampal herniations, but the cornu ammonis almost invariably shows anoxic changes.

The possibility of venous compression or laceration at birth must also be considered. The venous drainage of the superior and lateral surfaces of the temporal lobe is predominantly through the superficial and deep middle cerebral veins to the cavernous and superior petrosal sinuses. These anastomose freely with the superior cerebral veins, which drain to the superior longitudinal sinus (largely by way of the great anastomotic vein of Trolard) or through the inferior anastomotic vein of

9. Bardeen, C. R., and others: Manual of Human Embryology, edited by F. Kiebel, and F. P. Mall, Philadelphia, J. B. Lippincott Company, 1910-1912, Vol. 2, p. 623.

10. Abbie, A. A.: Clinical Significance of the Anterior Choroidal Artery, Brain **56**:233-246 (Sept.) 1933.

11. Alexander, L.: Vascular Supply of the Strio-Pallidum, A. Res. Nerv. & Ment. Dis., Proc. **21**:77-132, 1942.

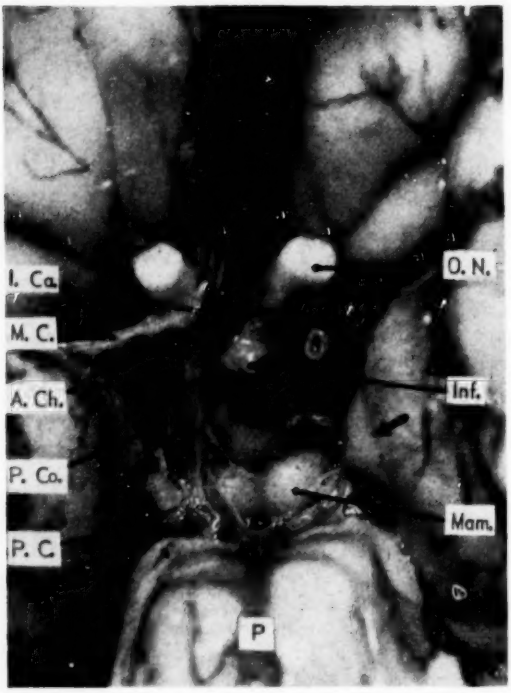

Fig. 7.—Basal view of the brain of a full-term newborn infant. The forceps are retracting the internal carotid artery (*I. Ca.*) medially. Note the comparative size of the anterior choroidal artery (*A. Ch.*), middle cerebral artery (*M. C.*), and branches of the posterior cerebral artery (*P. C.*) to the temporal lobe. The arrow indicates the normal groove on the hippocampal gyrus made by the free edge of the tentorium. *P. Co.* indicates the posterior communicating artery; *O. N.*, the optic nerve; *Inf.*, the infundibulum; *Mam.*, the mamillary bodies.

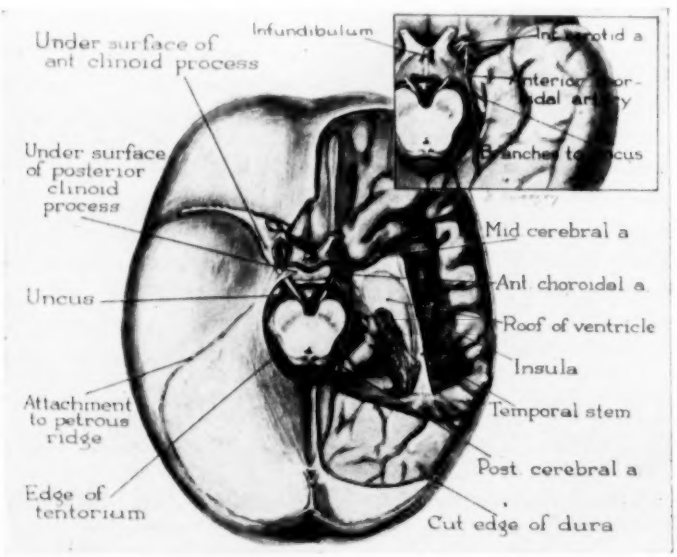

Fig. 8.—Drawing of the undersurface of the brain and dura, showing the relation of the uncus, hippocampal gyrus, and cerebral vessels to the incisura of the tentorium.

Labbé to the transverse sinus. The areas surrounding the inferior horn of the lateral ventricles, including the uncus, hippocampal gyrus, and cornu ammonis, drain through the internal cerebral veins or the basal venous system to the vein of Galen. In birth injuries the external or internal cerebral veins may be torn from their attachments to the dural sinuses (Courville[12]). Venous compression may account for some of the lesions seen in epileptic patients, but the commonest abnormality which we have described seems to be more easily explained on the basis of arterial compression.

Thus, the temporal lobe seems particularly susceptible to injury at birth from the standpoint of mechanical interference with its blood supply and of susceptibility to anoxic states. It is clear that the temporal lobe is susceptible to injury by anoxia, as pointed out by Spielmeyer. The arteries of supply to the mesial and inferior surfaces of the lobe cross the free margin of the tentorium. Herniation of the temporal lobe through the incisura of the tentorium, if it occurs at the time of birth, would produce ischemia of the herniated uncus and hippocampal gyrus and might also cause compression of the arteries and veins, particularly the anterior choroidal and the branches of the posterior cerebral artery to the inferior surface of the temporal lobe.

In the next section we shall demonstrate that extreme compression of the infant head as it passes through the birth canal must produce varying degrees of temporal lobe herniation.

HERNIATION OF THE BRAIN AT BIRTH

Because of the distribution of the abnormality in cases of incisural sclerosis, we have long suspected that severe pressure on the head of an infant at birth might produce herniation of the hippocampal regions, and it seemed likely that such herniation might reduce itself spontaneously when the pressure was released. It does not seem necessary to postulate that delivery was difficult or roughly handled or that forceps caused the damage, although these things undoubtedly occur at times. In fact, forceps were not used in some of our cases, and delivery was not considered difficult in others. Yet, smallness of the middle fossa of the skull was associated with atrophic areas of the temporal lobe, which areas were proved to become epileptogenic later in life.

We were troubled by the fact that we had not actually seen herniation of the hippocampal regions in routine autopsies of stillborn infants, although petechial hemorrhages were occasionally seen along the tentorial groove. Did the herniations reduce themselves spontaneously, or did we reduce them ourselves by removing the brain from above in the usual manner? The brain of the newborn is very soft, and the tentorium more elastic than that of the adult, so that spontaneous reduction certainly seemed possible.

We have recently been able to demonstrate the mechanism of herniation of the hippocampal regions by applying external pressure to the heads of stillborn infants

12. Courville, C. B.: Pathology of the Central Nervous System: A Study Based upon a Survey of Lesions Found in a Series of 15,000 Autopsies, Ed. 2, Mountain View, Calif., Pacific Press Publication Association, 1937, pp. 89-90, and 242-250.

which have come to the department of pathology. With the permission of Prof. G. Lyman Duff, we studied and carried out autopsy on these infants. Selecting full-term and premature infants who had died during or shortly before delivery, we applied pressure to the head by wrapping it with a rubber tube. We then froze the head solidly and made coronal sections with a saw. These sections showed that the uncus and medial part of the hippocampal gyrus had been forced over the free edge of the tentorium (Fig. 9). This could be done easily with pressures that would not tear the dura. Herniation of this portion of the cerebrum into the incisura of the tentorium is produced frequently by expanding lesions or brain edema above the tentorium in adults. But in such cases the continuing pressure

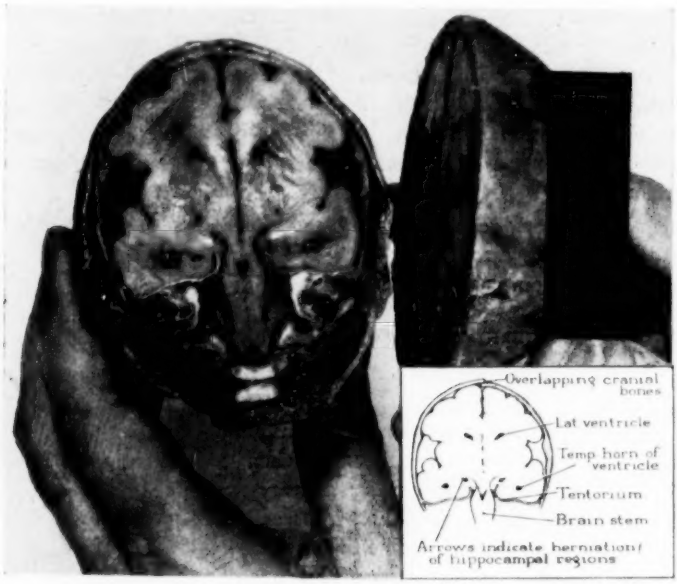

Fig. 9.—Photograph of the head of a premature stillborn infant which had been subjected to moderate pressure and frozen before being sawn in half. Note the overlapping of parietal bones. Arrows indicate marked herniation of the uncal regions over the free edges of the tentorium.

from above does not permit reduction of the herniation (Reid and Cone [13]; Schwarz and Rosner [14]).

However, if we applied the same pressure and then released it before freezing, we saw no evidence of herniation. This probably accounts for the fact that these herniations are not seen at routine autopsy, although they must occur frequently during birth and might well be a cause of death if the compression is too great. The

13. Reid, W. L., and Cone, W. V.: Mechanism of Fixed Dilatation of Pupil Resulting from Ipsilateral Cerebral Compression, J. A. M. A. **112**:2030-2034 (May 20) 1939.

14. Schwarz, G. A., and Rosner, A. A.: Displacement and Herniation of the Hippocampal Gyrus Through the Incisura Tentorii: Clinicopathologic Study, Arch. Neurol. & Psychiat. **46**:297-321 (Aug.) 1941.

vessels supplying the inferior and mesial surfaces of the temporal lobe are distorted and must be pressed against the free edge of the tentorium during the herniation. This could account for the sclerosis of those convolutions of the temporal lobe that are not included in the direct compression.

We have also been able to visualize the mechanism of herniation by removing the cerebellum and brain stem from below, leaving the cerebral hemispheres intact above, and applying pressure to the head. In both types of experiment, it was noted that both hippocampal gyri may be herniated, but that the protrusion of one is usually more marked than that of the other. Thus, bilateral lesions may occur, but one side is likely to be more severely damaged than the other. Such herniations were more easily produced in the case of premature infants than in those born at full term.

SUMMARY

A large proportion of all epileptics suffer from temporal lobe seizures, as demonstrated by electroencephalography. Seizures of this type continue into adult life, or may even begin then, although the cause is often to be found in the mechanism of birth compression. A discharging epileptogenic focus in various areas of the temporal cortex may produce a variety of initiating seizure phenomena. Thus, these attacks may be ushered in by abdominal auras, cephalic auras, olfactory auras, psychical hallucinations (or dream states), illusions of perception (e. g., déjà vu phenomena), and automatisms.

In a study of 157 cases in which seizures originated in the temporal lobe, various lesions were found on surgical exploration and radical excision. In 100 of these cases (63%) pathological study suggested compression or anoxia at birth as the cause of the lesions found. In the remaining 57 cases there was evidence of postnatal injury, intracranial infection, or neoplasm. The clinical histories frequently failed to provide reliable preoperative clues to the cause.

In the 100 cases in which the pathological findings suggested that the lesion was produced at birth, the gross lesions varied from atrophy or toughness of a single gyrus to atrophy of the entire temporal lobe and parts of the adjacent cortex. The gyri were often shrunken, yellow, avascular, and obviously smaller than normal. The uncus, hippocampal gyrus, and first temporal gyrus were the areas most frequently involved. This appeared so frequently that it seemed to form a pathological entity, which we have called incisural sclerosis. Histologically, the excised areas revealed an increase in fibrous astrocytes in the gray and white matter, with scattered zones of ganglionic destruction in some cases.

It has been pointed out above that the temporal lobe is poorly developed at the time of birth and may, in consequence, be more susceptible to damage by anoxia. It was pointed out also that the branches of the posterior cerebral, anterior choroidal, and middle cerebral arteries, which cross the free edge of the tentorium to supply the mesial and inferior surfaces of the temporal lobe, are so placed that temporal herniation at the time of birth would compress these arteries against the free edge. The anterior choroidal artery, which at birth is about as large in diameter as the middle cerebral artery, is especially vulnerable to such compression.

Finally, we have shown that compression of the heads of stillborn babies does produce temporal lobe herniation and that unless the head is frozen the evidence of this herniation disappears, so that it might well be missed during routine necropsy.

In conclusion, incisural sclerosis of the mesial and inferior portions of the temporal lobe is the pathological condition that is most frequently found in temporal lobe epilepsy. Histological study suggests that this partial destruction must have been produced by acute anoxia. We conclude that this sclerosis is produced by temporary herniation of the temporal lobe through the incisura of the tentorium at the time of birth. Such lesions ripen into epileptogenic foci so slowly that temporal lobe seizures may make their appearance many years after birth.

PROBLEMS IN SUPERVISION OF PSYCHIATRIC RESIDENTS IN PSYCHOTHERAPY

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THE RECENT expansion and extension of psychiatric residency programs are effecting a new orientation in such training programs. Formerly the focus of training activities centered in the inpatient service. With the gradual introduction of psychoanalytic concepts into psychiatry and with the development of dynamically oriented departments of psychiatry, the psychiatric outpatient clinic now occupies a key position in which psychotherapy can be studied. Psychiatric educators are particularly interested in the form and structure of training programs and necessarily must devote much attention to teaching methods. One of the most effective and most widely used teaching methods is the close supervision of the resident's clinical work in all areas of his training. Since the particular topic with which we are concerned is the supervision of the resident's work in psychotherapy, my observations will be limited to this aspect of supervision.

The young physician who seeks psychiatric training today desires a training center which offers more than the opportunity of studying a variety of psychiatric patients on an inpatient service. He is also interested in gaining experience of treating a varied group of ambulatory psychiatric patients in a setting in which he hopes to learn and develop psychotherapeutic techniques. The present-day psychiatric resident is more sophisticated in his psychiatric knowledge than his predecessors and has rather clearly defined ideas of what he expects in his training period. He is no longer satisfied with just being exposed to a mass of psychiatric cases but expects, and at times demands, the best possible type of supervision of his therapeutic endeavors by experienced and skilled psychotherapists.

As preparation for this report I polled our residents and many of our supervisors for their opinions, suggestions, and criticisms of the supervisory process and have included some of that material in this paper.

At present our residents are supervised in both group and individual sessions. A few of the senior staff carry the brunt of the group work, while practically the entire full-time, part-time, and visiting senior staff are engaged in individual supervision. Most of the residents preferred individual to group supervision, although several felt both types of supervision were important in their training. Each resident is assigned a senior staff psychiatrist as an individual supervisor for a period of three months and meets with him weekly for one or two hours. (There are

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Read at a round table symposium on "Supervision of Psychiatric Residents in Psychotherapy" at the Annual Meeting of the American Psychiatric Association, Atlantic City, N. J., on May 13, 1952.

obvious advantages and disadvantages in rotating the supervision on a three-month basis, and this question must be settled by experimentation.) Several of the residents preferred the continuous case method, in which one or two cases are presented over a long period of time, to the more usual method of covering the majority of their cases during the course of supervision. It seems advisable for both the resident and the supervisor to be flexible in deciding the mode of presentation.

GENERAL PROBLEMS IN INDIVIDUAL SUPERVISION

A discussion of the general problems of individual supervision should consider the supervisor as well as the resident. It is important, in those instances in which there is a large group of residents, that a few key members of the senior teaching staff be familiar with the skills, abilities, and personalities of the various psychiatrists who are selected as supervisors. There are marked individual differences in any group of able psychiatrists, so that it is possible for the resident to be exposed to various types of personalities and various points of view. The needs of the residents also vary considerably in terms both of their specific personalities and of their level of training. One of the tasks of the administrator is to pair the supervisor and the resident so that the resident can gain maximally from the experience. As an example, I may cite one of our supervisors who is usually assigned to first-year residents. He is a very able psychiatrist, who is engaged in the general practice of psychiatry and is a warm, kindly, benevolent, and nonthreatening person. The first-year residents assigned to him feel very comfortable in their sessions and gain necessary emotional support and security. However, "advanced" residents who are interested in developing more highly specialized therapeutic techniques might benefit less in working with this particular supervisor. This example leads into the area of status within the supervisor group from the residents' point of view. The residents soon learn who are the best supervisors and press the administrator to assign them to teachers of their own choices. This pressure can create additional problems for the administrator and calls for frequent reviews of the supervisory staff. Regularly scheduled meetings of the teaching staff are held to discuss progress and problems of the residents, but it is also possible in this type of conference to evaluate the skills of the supervisors. The free exchange of ideas among them can also serve as a learning experience for the supervisor himself.

The supervisor should not be placed in a position of assuming an administrative role in the functioning of a clinical unit. Although he should be fully acquainted with the general structure and functioning of the clinical unit in which the residents operate, he should refer problems of an administrative nature to those members of the department who are in close and active contact with the day-to-day functioning of the clinical unit.

Many residents experience more anxiety when they start psychotherapeutic work with ambulatory patients than when they are assigned to an inpatient service. The inpatient service offers more security to the resident, since there are others who share in the responsibility of the total handling of the patient; immediate help is available when difficulties or emergencies arise, and the situation is more similar to his previous experience as an intern. When the resident undertakes psychotherapy with clinic patients, he is more on his own and is attempting to master therapeutic techniques which are far less structuralized and stereotyped than the

therapeutic techniques used in an inpatient service. Another anxiety-producing factor is that the first-year resident often approaches supervision in terms of his medical school period, in which certain clinical teachers were cool critics, rather than interested, more experienced colleagues. Such a misconception of the role of the supervisor may create initial blocks because of the fear of being caught in making mistakes and the consequent need to be protected from feelings of failure. These attitudes may also block discussion of countertransference problems until the resident learns that countertransference is not a mistake but a phenomenon. Therefore the first goal, and perhaps the most important one, in supervision is to relieve or reduce the anxiety of the resident, so that the learning process is not blocked and growth and maturation can occur. Most of our residents mentioned that one of the most important areas in which help was given was that they became less anxious in doing psychotherapy.

The anxiety of the resident may not be revealed directly, but often creates a resistance in the supervisory process. The resistances appear in many forms, e. g., tardiness, forgetting the appointment, or filling the hour with nonessential material. As an example, I may cite an incident with a resident who came to us in his third year of training for the specific purpose of undertaking psychotherapy with ambulatory patients under close supervision. I supervised him during his second period and noticed that in his first two sessions with me he brought in three or four cases, each of which he presented quite briefly. On his third visit I asked him how the previous supervisory hours had been conducted and was told that he usually discussed three or four patients each time. I commented on this and pointed out that he was using this technique to avoid becoming involved in the supervisory process, and then he revealed considerable anxiety in relation to his clinic assignment. The usual feelings of inadequacy, inferiority, and unfavorable comparison with other residents were ventilated, and after this material was handled and discussed in a reassuring manner he was able to present one case at a time for more thorough discussion and his anxiety in conducting psychotherapy diminished considerably.

The attitudes of supervisors toward residents vary from a passive, reassuring "Everything is OK," to competitive, hostile, belittling, and generally destructive ones. The supervisor should be a professionally and emotionally secure person with whom the resident can identify as an able and honest psychiatrist. He must have enough insight into how he functions as an individual so that his own irrational needs and defenses do not create blocks in the supervisory process or create further problems for the resident. Resistance to supervision developing from anxiety can also take place in him. When he finds he is frequently late or frequently cancels the appointment or is overly passive or overly aggressive in the sessions, he should look into himself and attempt to understand what is creating his own resistance in supervision.

In addition to being well trained, a supervisor should be actively engaged in psychotherapy with patients, and his psychotherapeutic techniques should be flexible. For instance, if he is an analyst, he should have the experience of dealing with patients in brief psychotherapy. Some time ago one of the residents presented a patient to an eminent analyst who was visiting the department and who strongly, but quite unrealistically, recommended that this particular patient be seen three

times each week in analytic therapy. The visiting psychoanalyst overlooked the fact that the available clinical facilities were such that it was impossible to carry out such a recommendation, which then did nothing but increase the anxiety of the resident who was treating the patient.

The focus of discussion during individual supervision may be patient-oriented; process-oriented, with emphasis on the dynamics of the doctor-patient relationship, or therapist-oriented, with emphasis on the dynamics of the supervisor-resident relationship.[1] Usually all three areas are covered, and the decision as to which area should be emphasized depends on the needs of the individual resident, the needs of the patient, and the particular skills and interests of the supervisor.

PATIENT-ORIENTED SUPERVISION

In some training centers which emphasize psychoanalytically oriented psychotherapy, a good deal of emphasis is placed on the psychodynamics and genetic factors in an individual case, and at times too little attention is devoted to the exactness of clinical diagnosis. The lure and mysteries of psychodynamics become so attractive to the resident that there is a tendency to avoid facing and learning the intricacies and complications of clinical diagnosis. In some instances these same attitudes blind the resident to the importance of understanding the details and stresses of the current life situation of the patient. These often-neglected areas in the residents' clinical work should be emphasized in the supervisory session, and the resident should be helped in sharpening his clinical acumen. This discipline will aid him considerably in arriving at a working formulation of a case early in therapy, to establish goals of therapy, and to gather and integrate data for a therapeutic prognosis.

In some clinics certain fixed rituals of conducting psychotherapy have developed in regard to the frequency and length of time of interviews. Once any set of rigid rules for conducting psychotherapy is established, it is not surprising that residents accept such patterns in a compulsive manner. The tragedy is not that the resident incorporates such rituals, but that many supervisors blindly follow the same pattern and the resident does not have an opportunity of developing flexibility through experimentation by trial and error in his psychotherapeutic techniques.

At times the supervisor is at a disadvantage in evaluating a patient because he has not had a direct opportunity to examine the patient. Opportunities should be available for the supervisor to interview a patient, either alone or with the resident if indicated. Certainly, patient-oriented supervision must emphasize psychodynamics and genetic factors, but not to the exclusion of clinical diagnosis. The majority of our residents believed that understanding of the psychodynamics of a case was the area in which most help was given in supervision.

PROCESS-ORIENTED SUPERVISION

The doctor-patient relationship is undoubtedly the most important single factor in the psychotherapeutic process, and as such deserves much attention during supervision. The area of transference is, of course, a complicated one, and obviously

1. Modlin, H.: Supervision, in Psychiatric Residency Training Program, Group for Advancement of Psychiatry Report, to be published.

the various ramifications of this phenomenon cannot be covered at this time; I shall only highlight those areas in which difficulties commonly arise. Some residents do not understand that transference manifestations represent irrational, unconscious attitudes of a patient to the therapist but, instead, talk about transference quite glibly in terms of whether the patient likes or dislikes them. Some residents handle their anxiety about transference by early and immediate transference interpretations, which usually represent their own defense against transference involvement.

When the topic of transference is discussed, it is quite natural that countertransference phenomena must be looked for and discussed. Here, too, the resident often equates countertransference with whether he likes or dislikes the patient and must learn that countertransference is a complicated process and includes the therapist's own unconscious and irrational attitudes to the patient aroused during various phases of treatment. In a secure supervisor-resident relationship one can demonstrate many countertransference manifestations to the resident. Although at times certain delicate problems may be exposed, one can avoid stimulating too much anxiety in the resident, as well as placing him in a position of a patient rather than of a student. However, in the face of certain types of countertransference attitudes which are creating major difficulties in the learning process and in the resident's therapeutic abilities, it may be necessary to advise him to seek the proper therapeutic help in overcoming his own emotional sensitivities.

DYNAMICS OF THE SUPERVISOR-RESIDENT RELATIONSHIP

The supervisor-resident relationship has all the characteristics of a teacher-student relationship, in addition to the various rational and irrational emotional attitudes that exist in a doctor-patient relationship. It has already been stated that one of the chief goals of the supervisor-resident relationship is to reduce and relieve the anxiety of the resident so that he can learn and grow in his psychotherapeutic skills. The resident, like a patient, may come to the sessions not with an idea of sharing in a learning experience but, rather, with expectations of magical help from an omniscient and omnipotent supervisor. The real misfortune occurs when the supervisor, for reasons of his own, accepts this role and becomes the prophet rather than the teacher. Some residents think of the supervisor as a "control," and the very inherent meaning of the word "control" reveals the underlying emotional attitudes of the resident. Obviously, if the supervisor assumes the role of a "control," it is likely that the residents will become so defensive that real progress in learning and growth is blocked.

The mature supervisor should be able to instill confidence and a sense of security in the resident without avoiding or minimizing the realistic difficulties and limitations of psychotherapy as it exists at the present time. Occasionally he will be in a position to "drop a pearl" or "hit the jack pot" in making "the correct interpretation at the correct time," but oftener than not such dramatic occurrences do not happen. All experienced therapists have had failures with various types of patients, and should have developed realistic appraisals of their own abilities and understanding of the limitations of the tools with which they work. They should have enough self-confidence to indoctrinate the residents with realistic attitudes toward psychotherapy, rather than cover up their own feelings of inadequacy or project their omnipotent wishes onto the residents.

Some supervisors believe that the most important aspect of the supervisor-resident relationship is therapeutic, and undoubtedly this is inherent in a good supervisor-resident relationship in its broadest sense; but it is our opinion that a therapeutic relationship can exist without the resident being treated as a patient. Probably the best safeguard in the relationship is that the supervisor must share a learning experience with the resident. He should have enough wisdom and humility to recognize that the progress of the resident will depend much more on his inherent capacity to learn than on what the supervisor can "teach." There should be a keen appreciation that what he represents as an object of identification to the resident is more important than what he imparts as factual knowledge. He must realize that individual supervision is only one aspect of the training program and that in the final analysis a resident becomes a good psychiatrist because of the impact of the total training program rather than because of any one particular teacher or teaching session. The supervisor must have respect for the student's potential capacities and abilities to develop gradually his own psychotherapeutic skills in the setting of continuous experience with psychiatric patients. It is in such a supervisor-resident relationship that a sense of freedom can develop which allows for the expression of sincere and honest opinions and feelings, so essential for professional and personal growth.

INFECTIOUS MONONUCLEOSIS WITH DIFFUSE INVOLVEMENT OF NERVOUS SYSTEM

Report of a Case

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ALTHOUGH infectious mononucleosis was first described by Pfeiffer [1] in 1889, it was not until 1931 that its manifestations referable to the nervous system were recognized.[2] Since then at least 36 reports, describing 54 patients, have appeared on this unusual manifestation of the infection. The following case of infectious mononucleosis with involvement of the central nervous system presents unusual clinical findings, and for the first time a positive result of a quantitative heterophile agglutination test on the cerebrospinal fluid is reported. Electroencephalographic tracings taken during the course of acute illness are also demonstrated.

REPORT OF CASE

An airman aged 21, white, had an infection of the upper respiratory tract on March 31, 1952. Four days later there developed recurrent frontal headaches, which were most severe during the morning. Thereafter he noted easy fatigability, malaise, and lethargy. On the evening of April 9 he had a severe chill, followed by profuse diaphoresis, and on the following day he was extremely lethargic and vomited several times. During the day he seemed to be somewhat irrational. That evening he had an episode of twitching of the left side of the face and deviation of the eyes to the left. This attack lasted only a few seconds. A similar seizure occurred on the following day. At noon on April 13 he suddenly fell backward and had a generalized convulsion. He then became restless, irrational, and semistuporous. At a nearby hospital he was found to have meningismus and fever. Several atypical lymphocytes were noted on a stained blood smear. Transfer to this hospital was effected.

On examination the patient appeared acutely ill and semicomatose and thrashed about aimlessly whenever subjected to the slightest stimulus. Inappropriate response, wild shouting, and aggressive behavior occurred after any stimulus. The rectal temperature was 102.2 F.; the pulse rate was 116 per minute; the respirations were 20 per minute. The blood pressure was 116/58. The anterior and posterior cervical lymph nodes, as well as the axillary lymph nodes,

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1. Pfeiffer, E.: Drüsenfieber, Jahrb. Kinderh. **29**:257-264, 1889.

2. Epstein, S. H., and Dameshek, W.: Involvement of the Central Nervous System in a Case of Glandular Fever, New England J. Med. **205**:1238-1241 (Dec. 24) 1931. Johansen, A. H.: Serous Meningitis and Infectious Mononucleosis, Acta med. scandinav. **76**:269-272, 1931.

were enlarged and firm. Babinski, Chaddock, and Oppenheim signs were elicited on the left, but not on the right. The reflexes were otherwise physiological.

The following laboratory data were obtained: Serologic reactions of the blood for syphilis were negative. The urine was normal. The CO_2-combining power and the serum sodium, potassium, and chlorides were normal. Roentgenograms of the chest, skull, and sinuses revealed nothing abnormal. The hemoglobin measured 12.3 gm. per 100 cc. The hemogram showed 14,300 white cells per cubic millimeter, with 31% polymorphonuclear leucocytes, 61% lymphocytes, 7% monocytes, and 1% eosinophiles. Many atypical lymphocytes were noted on the stained blood smear. The sedimentation rate was 18 mm. in one hour (corrected, Wintrobe). Repeated hemograms on ensuing days showed a very gradual return to normal, so that on May 6 the white blood cell count and differential count were normal and no atypical lymphocytes were seen. A blood culture was sterile. Spinal fluid withdrawn by lumbar puncture on the day of admission was under normal pressure, was clear, and showed no cellular elements. The spinal fluid protein was 195 mg. and the sugar 79 mg., per 100 cc.

On April 16 the spinal fluid was again grossly clear and under normal pressure but contained 25 lymphocytes per cubic millimeter. The total protein was 154 mg. per 100 cc.; the colloidal gold curve was normal, and the Wassermann reaction was negative. On the following day the fluid was grossly clear and under normal pressure and contained 10 lymphocytes per cubic millimeter. The spinal fluid protein, however, had risen to 474 mg. per 100 cc., and the colloidal gold curve was 541000000. A qualitative heterophile agglutination test made on this fluid, according to the method described by Silberstein and associates,[3] gave a 4+ reaction with both sheep red blood cells and guinea pig kidney and a negative reaction with boiled beef red blood cells. A quantitative heterophile agglutination test performed on the same fluid, according to the method of Paul and Bunnell,[4] gave a positive reaction in a titer of 1:28 with both sheep red blood cells and guinea pig kidney. The results of the blood heterophile agglutination test on the same day were positive in a titer of 1:1,792 at two hours and in a titer of 7:3,584 overnight. Forssman antibodies were absorbed.

At the time of discharge from the hospital, one month after admission, the patient's blood still demonstrated a positive reaction to the heterophile agglutination test in a titer of 1:448 at two hours and of 1:896 overnight. On May 8 the spinal fluid was entirely normal except that the qualitative heterophile agglutination test was still strongly positive with sheep red blood cells and guinea pig kidney and negative with boiled beef red blood cells. The quantitative agglutination test was now negative, and the spinal fluid protein was normal.

Virus studies on paired specimens of spinal fluid gave negative results for western equine encephalitis, St. Louis encephalitis, lymphocytic choriomeningitis, and mumps encephalitis.

For the first 24 hours after admission the patient continued to be disturbed and irrational. He was given penicillin and symptomatic treatment. At 7 p. m. on April 14 he suddenly became rational and fairly well oriented. He had amnesia for the events of the preceding two days, complained of lethargy, weakness, and retro-orbital headache, and for the next several days experienced considerable difficulty in coordinating the movements of his legs. He showed considerable restlessness, and his affect was frequently inappropriate. He became afebrile on the third hospital day. One week after admission he was completely asymptomatic and fairly alert, and the physical findings were entirely normal. No further symptoms occurred until the time of discharge, on May 14, 1952.

An electroencephalogram taken on the fifth day of hospitalization was interpreted as showing marked generalized abnormality, resembling that of encephalitis (Fig. 1). Another tracing, done on May 12, was interpreted as essentially normal (Fig. 2).

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3. Silberstein, J. K.; Bernstein, T. C., and Stern, T.: Demonstration of Heterophile Antibodies in the Cerebrospinal Fluid from Patients with Infectious Mononucleosis, J. Lab. & Clin. Med. **33**:1204-1206 (Oct.) 1948.

4. Paul, J. R., and Bunnell, W. W.: Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90-104 (Jan.) 1932.

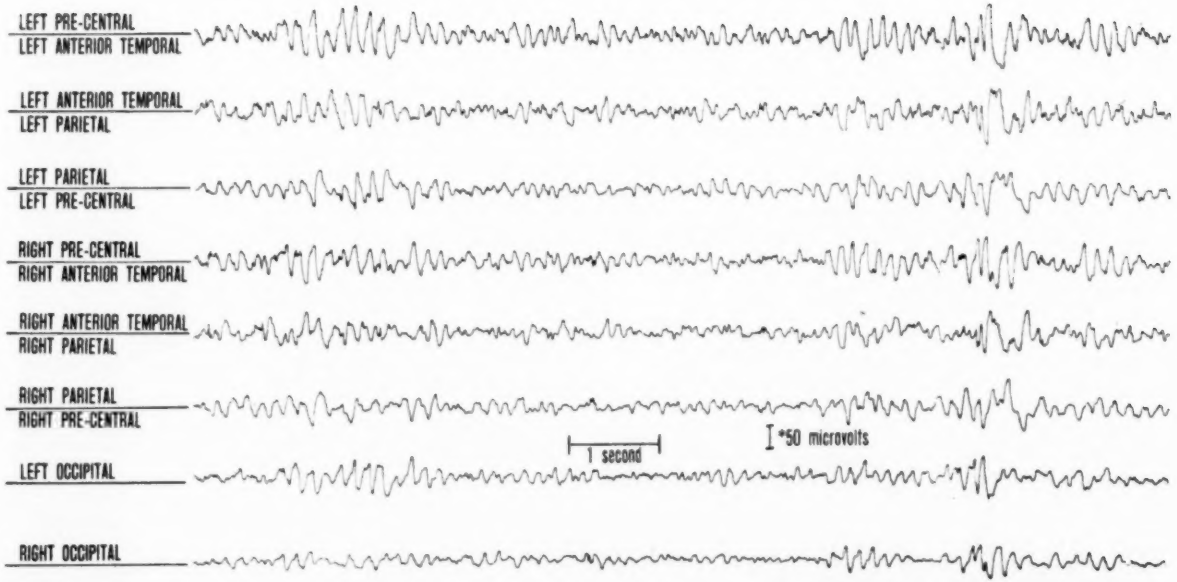

Fig. 1.—Section from electroencephalographic tracing taken on third day of hospitalization. The rhythm is markedly irregular, with paroxysmal 7 to 8 cps activity occurring over the entire head. Occasionally an even slower rhythm is interspersed through this pattern. The basic alpha rhythm is almost completely suppressed. No evidence of focal activity is present anywhere in the tracing.

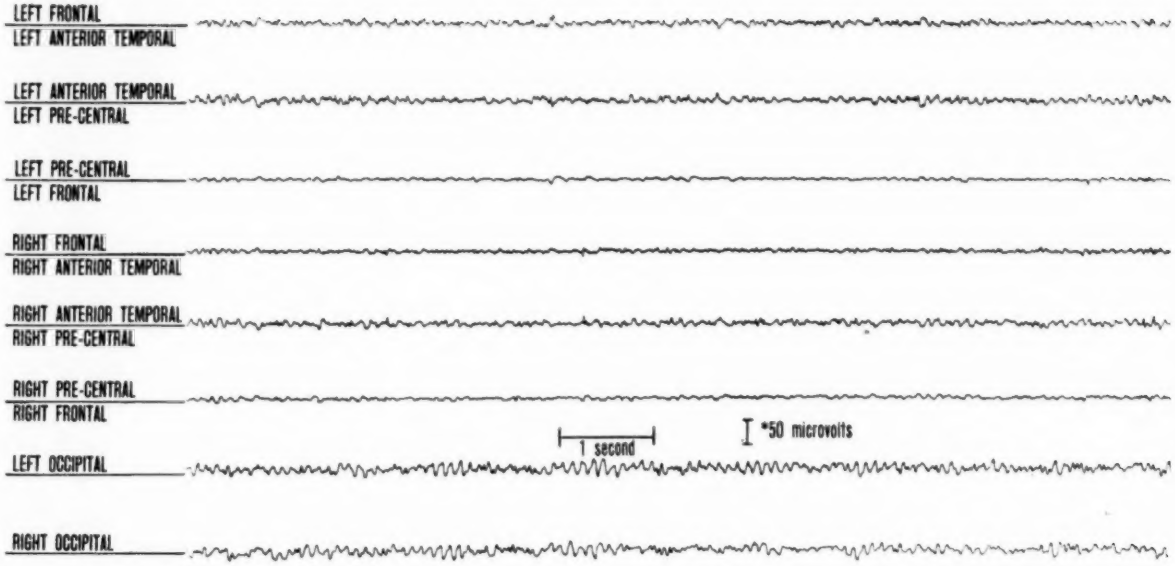

Fig. 2.—Section from electroencephalogram taken on the 24th day of hospitalization. The basic alpha rhythm is restored. Some low-voltage fast activity is present; otherwise, the tracing is an essentially normal one.

COMMENT

When the predominating feature in a case of infectious mononucleosis is involvement of the central nervous system, any of several clinical patterns may appear. Bernstein and Wolff, in a review of 34 such cases,[5] stated that a syndrome clinically resembling that of acute meningitis occurred in 10 patients. Four others had symptoms of diffuse encephalitis, and a similar number appeared to have meningoencephalitis. There were seven patients with encephalitis or meningitis followed by an acute polyneuritis suggestive of Guillain-Barré disease. Six had isolated peripheral neuropathy. In more recent cases[6] similar clinical characteristics were exhibited. Our patient presented a diffuse encephalitis.

With the great variety of clinical syndromes observed, it is not surprising that many unique signs of neurologic involvement have been recorded.[6g] These include ptosis, anosmia, bilateral papilloretinal edema, ocular paralyses, inability to chew, numbness of the face, bilateral facial paralysis, dysarthria, and dysphagia. Convulsions have been reported in seven instances, but recurrent seizures have been described only twice. Field[7] reported a case similar to our own in which a generalized convulsion followed a Jacksonian seizure.

Owing to the benign course of the illness, few pathologic examinations have been made on patients with infectious mononucleosis who exhibited symptoms referable to the central nervous system. Among the variety of lesions noted in three patients studied were perivascular cuffing and perivascular and pericellular edema in the cerebral cortex; focal degenerative changes in the Purkinje cells of the cerebellum, and congestion, edema, and mononuclear infiltration of cranial nerve nuclei and medullary centers.[8] In another report,[9] examination of the brain was performed on a patient who died in an airplane crash one month after being ill with infectious mononucleosis without gross clinical involvement of the central nervous system. Prominent perivascular cuffing was noted in the cerebral cortex.

5. Bernstein, T. C., and Wolff, H. G.: Involvement of the Nervous System in Infectious Mononucleosis, Ann. Int. Med. **33**:1120-1138 (Nov.) 1950.

6. (*a*) Dolgopol, V. B., and Husson, G. S.: Infectious Mononucleosis with Neurologic Complications: Report of a Fatal Case, Arch. Int. Med. **83**:179-196 (Feb.) 1949. (*b*) Hoyne, R. M.: Involvement of Central Nervous System in Infectious Mononucleosis: Report of a Case with Ataxia and Nystagmus, Arch. Neurol. & Psychiat. **63**:606-610 (April) 1950. (*c*) McNeel, L.: Infectious Mononucleosis with Severe Meningoencephalitic Complications: Report of a Case, Wisconsin M. J. **50**:159-160 (Feb.) 1951. (*d*) Piel, J. J.; Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis of Central Nervous System with Bilateral Papilledema, J. Pediat. **37**:661-665 (Oct.) 1950. (*e*) Graham, S. D.; Schwartz, W. H., and Chapman, W. L.: Infectious Neuronitis Complicating Infectious Mononucleosis, U. S. Nav. M. Bull. **49**:914-919 (Sept.-Oct.) 1949. (*f*) Creaturo, N. E.: Infectious Mononucleosis and Polyneuritis (Guillain-Barré Syndrome): Report of a Case of Facial Diplegia Treated with 2, 3-Dimercaptopropanol (BAL), J. A. M. A. **143**:234-236 (May 20) 1950. (*g*) Hubler, W. L.; Bailey, A. A.; Campbell, D. C., and Mathieson, D. R.: Infectious Mononucleosis with Predominantly Neurologic Manifestations: Report of a Case, Proc. Staff Meet., Mayo Clin. **26**:313-320 (Aug. 15) 1951.

7. Field, W. W.: Infectious Mononucleosis with Severe Central Nervous System Involvement, Am. J. Med. **4**:154-157 (Jan.) 1948.

8. Dolgopol and Husson.[6a] Custer, R. P., and Smith, E. B.: Pathology of Infectious Mononucleosis, Blood **3**:830-857 (Aug.) 1948.

9. Allen, F. H., and Kellner, A.: Infectious Mononucleosis: An Autopsy Report, Am. J. Path. **23**:463-477 (May) 1947.

The markedly abnormal electroencephalographic record obtained early in the course of hospitalization contrasts strongly with the relatively normal tracing obtained just prior to discharge of the patient from the hospital. This is in accord with the clinical picture of acute diffuse encephalitis.

Numerous attempts to obtain a positive reaction of the cerebrospinal fluid with the standard Paul-Bunnell test have been uniformly unsuccessful.[10] In 1948, Silberstein and associates,[3] employing large volumes of spinal fluid and using dilute sheep erythrocyte suspensions as antigens, described a qualitative heterophile agglutination test which gave a positive reading in six cases of infectious mononucleosis. The standard quantitative test was not performed. The extremely strong reaction of the spinal fluid in our case when tested by the Silberstein procedure appears to substantiate the activity of this method. In addition, a positive titer of the spinal fluid with the Paul-Bunnell test was recorded and is reported for the first time. The low titer of 1 : 28 in the face of the strongly positive qualitative test and the severe illness of the patient reemphasize the relative insensitivity of the cerebrospinal fluid to the heterophile agglutination phenomenon. This impression is further substantiated by the rapid return to a negative result in the quantitative test within three weeks.

Tidy has stated that in cases in which involvement of the nervous system is severe the changes in the blood picture tend to be delayed.[11] In the case presented many atypical lymphocytes were noted on the blood smear and a strongly positive reaction in the Paul-Bunnell agglutination test was obtained while neurologic involvement was maximum. When characteristic blood changes are absent, diagnosis of infectious mononucleosis with involvement of the central nervous system becomes a difficult problem, particularly because of the variety of clinical syndromes which may occur. The disease should be considered in every case of infection of the central nervous system of obscure etiology.

SUMMARY

A case of infectious mononucleosis with predominant involvement of the central nervous system is presented. A positive result in the Paul-Bunnell quantitative heterophile agglutination test on the cerebrospinal fluid is reported for the first time. An abnormal electroencephalogram with typical changes of encephalitis is recorded; a later tracing was essentially normal. The necessity for considering infectious mononucleosis as a possible cause of any obscure infection of the nervous system is noted.

10. Schmidt, V., and Nyfeldt, R.: Regarding Infectious Mononucleosis and Meningo-Encephalitis, Acta oto-laryng. **26**:680-688, 1938. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of a Case, J. A. M. A. **116**:2482-2484 (May 31) 1941. Slade, J. deR.: Involvement of Central Nervous System in Infectious Mononucleosis: Report of 2 Cases, New England J. Med. **234**:753-757 (June 6) 1946. Schneider, T., and Michelson, D. A.: Central Nervous System Manifestations of Glandular Fever, South African M. J. **21**:57-60 (Jan. 25) 1947. Hubler and others.[6g]

11. Tidy, H.: Infectious Mononucleosis, Blood **3**:823-829 (Aug.) 1948.

DIAGNOSTIC AND THERAPEUTIC CLUES IN THE STUDY OF TETANUS

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DESPITE the infrequency of tetanus in clinical practice, the disease remains a major problem of therapy. Treatment in the past has consisted of the continued administration of sedative drugs. As a result, complications, such as hypoxia, pneumonia, and exhaustion, were difficult to prevent. Severe seizures usually cannot be arrested by sedation alone.

Simultaneous electroencephalographic and electromyographic studies can be used to differentiate tetanus from other conditions. Seizures of tetanus do not originate from the cortex, and hence produce no change in the electroencephalogram. If, at the same time, recordings are made from the involved muscles, prolonged bursts of 30 to 60 cps discharges can be seen whether the spasms be spontaneous or induced. This combination of unaltered brain waves and the typical myographic response during a convulsion would seem to point to the diagnosis of tetanus.

A therapeutic clue is offered by the effect of curare preparations on the electroencephalogram and the electromyogram. There is no appreciable change in the electroencephalogram (Fig. 2) in doses sufficient to abolish the muscle response as seen in the myogram, provided significant respiratory distress has not been induced. On the other hand, delta activity becomes prominent when sedative drugs are used (Fig. 1). In consideration of these facts, attempts have been made initially to determine for the patient with tetanus the point of abolition of the seizures, using tubocurarine chloride U. S. P. intravenously. The electromyogram was used as an additional control to clinical observation. Furthermore, efforts have been made to maintain this end-point of no seizures and absence of respiratory embarrassment by the subsequent administration of sufficient curare at regular intervals.

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The first use of curare in tetanus appears to have been by Wells,[1] who employed a crude preparation called "woorara." Many authors [2] have subsequently reported on the use of curare preparations and drugs with muscle-relaxing potentialities, such as mephenesin. Because of the relief of spasm and production of paralysis by a peripheral action, without initial respiratory involvement, curarization would seem to approach the ideal, providing the effect can be controlled satisfactorily. The relative evanescence of its action and the difficulties in prevention of overdosage are the main objections and have caused some to advise against its use.[3]

METHODS

Thirteen patients with tetanus were studied by simultaneous electroencephalographic and electromyographic recordings, using a Grass ink-writing oscillograph. Eleven scalp and two ear electrodes were applied in the usual standard positions. For the electromyograms needle electrodes were inserted into the maximally involved muscles, usually the abdominal, paravertebral, and masseter groups. The pulse rate, respiration rate, and blood pressure were taken at frequent intervals. Seizures were induced by various stimuli, including sudden noise, flickered light, and pain.

Five of the 13 patients were given tubocurarine intravenously, in small doses at frequent intervals, in an attempt to determine the optimum periodic, usually hourly, dose. The amount necessary at the initial procedure to abolish seizures clinically and electrically without respiratory embarrassment was used as a guide to the maximum dose needed subsequently. This was found to be from one-third to one-half the initial "titration" amount.

A skilled anesthetist was always present and helped in the original "titration." Means were at hand to have adequate continuous control of respiration and to permit removal of mucus. Free access to a vein either by a needle or by a plastic cannula attached to a tube providing a slow, continuous drip of saline was previously arranged.

Two patients were successfully maintained on repeated doses of curare for a period up to two weeks without the use of large amounts of sedative drugs, and their cases are reported in detail.

1. Wells, T. S.: Three Cases of Tetanus in Which "Woorara" Was Used, Proc. Roy. M. & Chir. Soc. **3**:142, 1859.

2. (*a*) Adriani, J., and Ochsner, A.: Some Observations on the Use of Curare in Treatment of Tetanus, Surgery **22**:509-515, 1947. (*b*) Binger, G. G., and Devnich, G.: Treatment of 2 Cases of Tetanus with *d*-Tubocurarine Chloride in Peanut Oil with Myricin, Anesthesiology **11**:199-205, 1950. (*c*) Browne, E. Z., and Stone, H. A.: Use of Curare in Tetanus, New Orleans M. & S. J. **100**:382-383, 1948. (*d*) Cole, L.: Tetanus Treated with Curare, Lancet **2**:475-477, 1934; (*e*) Treatment of Tetanus by Curare, Brit. M. J. **1**:125-126, 1935. (*f*) Cullen, S. C., and Quinn, C. S.: Use of Curare in Treatment of Tetanus: Case Report, Surgery **14**:256-260, 1943. (*g*) Godman, H. E., and Adriani, J.: Management of Patients with Tetanus: Some Clinical Experiences with Various Muscle-Relaxing Agents, J. A. M. A. **141**:754-756, 1949. (*h*) Goodman, E. G., and Reinhardt, J. F.: Postabortal Tetanus: Successful Treatment with Dihydro-Beta-Erythroidine, South. M. J. **36**:737-738, 1943. (*i*) Godman, H. E.: Mephenesin as a Relaxing Agent in Treatment of Tetanus: Clinical Experience in 12 Cases, California Med. **74**:126-127, 1951. (*j*) Hanna, C. B.: Use of Curare (Intocostrin) in Reducing Convulsive Effects of Tetanus, J. South Carolina M. A. **42**:5-8, 1946. (*k*) Macrae-Gibson, N. K.: A Case of Tetanus with Review of the Cases at Guy's Hospital 1929-49, Guy's Hosp. Rep. **99**:48-61, 1950. (*l*) Mitchell, J. A.: A Case of Tetanus Treated with Curarine, Lancet **1**:262, 1935. (*m*) Moseley, V.; Coleman, R. R., and Ellison, H.: Management of Tetanus with Mephenesin, J. South Carolina M. A. **46**:311-313, 1950. (*n*) Ory, E. M., and Grossman, L. A.: Management of Tetanus with Curare: Report of 2 Cases, Am. J. M. Sc. **215**:448-450, 1948. (*o*) Pryor, W. W., and Smith, D. T.: Case of Tetanus Treated with Antitoxin and *d*-Tubocurarine, Ann. Int. Med. **32**:728-730, 1950. (*p*) Santemma, E. E., and Graham, G. C.: Tolserol in Tetanus, New York J. Med. **50**:2731-2733, 1950. (*q*) West, R.: Intravenous Curarine in the Treatment of Tetanus, Lancet **1**:12-16, 1936.

3. Adriani and Ochsner.[2a] Goodman and Reinhardt.[2h]

REPORT OF CASES

CASE 1.—R. S., a youth aged 14, was hospitalized on June 28, 1951, because of difficulty in opening his mouth and generalized muscular stiffness. On June 7 he had sustained an abrasion of the right elbow, which was cleaned by his father and which healed without local complications. On June 22 he began to complain of stiffness in the back and neck and had difficulty in opening his mouth. Symptoms were progressive, so that by the time of admission there was pronounced stiffness of the back and abdomen and he was unable to eat or drink.

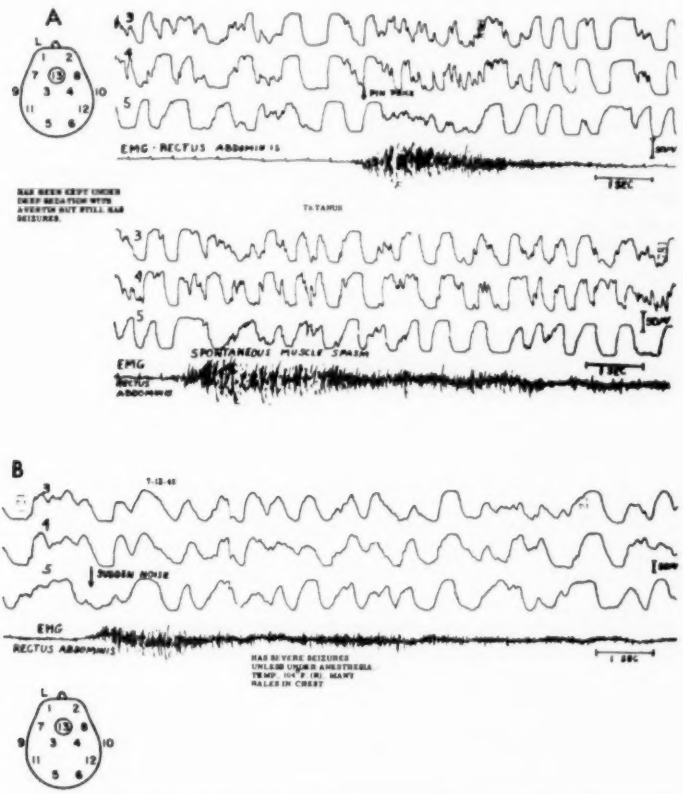

Fig. 1.—Electroencephalographic and electromyographic records for a 9-year-old girl with tetanus who was under sedative therapy with tribromoethanol (avertin®). Seizures continued even when the patient was under deep anesthesia. The electromyograms were recorded from the rectus abdominis. *A*, 11 days after onset of tetanus, and two days after initiation of sedation. Note (1) bursts of muscle potentials in the myogram during spasm induced by pinprick (upper tracing) and appearing spontaneously (lower tracing); (2) lack of significant alteration in the electroencephalogram during the seizure of tetanus, confirming noncortical origin; (3) delta activity, which appears in patients under deep sedation. *B*, three days later, with the patient under deeper sedation. Seizures could still be precipitated by sudden noise. Pulmonary complications had appeared, and the temperature rose to 104.0 F. (rectal). The very slow electroencephalographic activity would appear to reflect the depth of narcosis and/or the severity of complications.

Examination revealed an alert, well-developed boy who tended to assume the opisthotonic position. The temperature was 99.0 F. (rectal); the pulse rate, 100 per minute, and the blood pressure, 110/70. When he was placed on his back, the lumbar portion of the spine was elevated at least 6 cm. from the surface of the table. He was able to open his jaws only slightly during

periods of relative relaxation. When he was stimulated by touching or by noise, his head drew back, the jaws clenched, and the abdomen and thorax became rigid. These opisthotonic seizures would last from 10 seconds to 4 minutes. Muscular rigidity and spasms were most pronounced in the trunk and upper extremities. If individual muscles were tapped lightly, localized spasms could be induced involving parts of the muscle for periods of 10 seconds or more. Stretch reflexes were generally hyperactive, and there was bilateral unsustained ankle clonus. The remainder of the general physical and neurological examination was not remarkable.

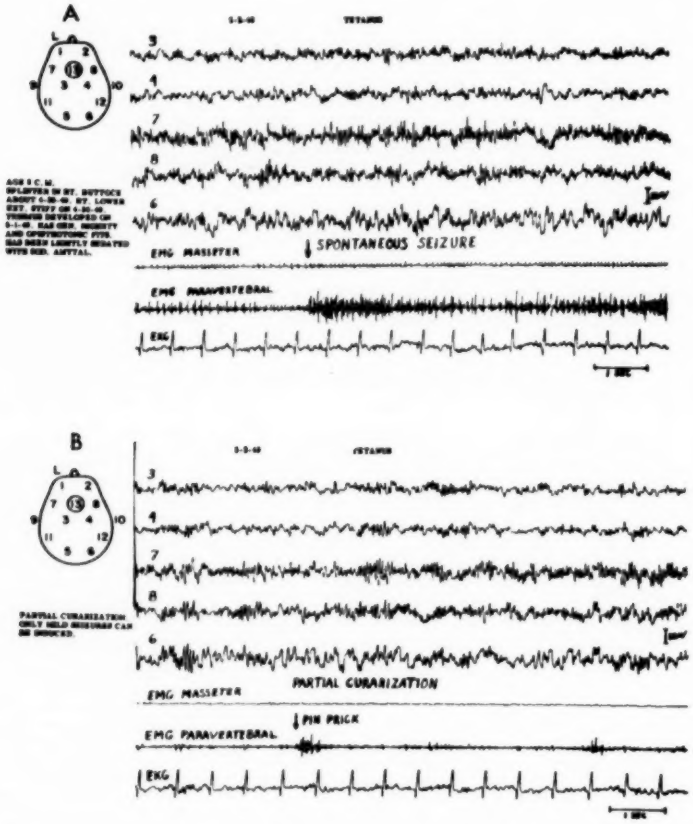

Fig. 2.—Electroencephalographic and electromyographic records from an 8-year-old boy with tetanus, showing the effect of a seizure and response to curare. The patient was having frequent opisthotonic fits and was under light sedation with amobarbital sodium. *A*, during a spontaneous seizure, which occurred at the arrow. Note (1) the burst of muscle potentials in the paravertebral electromyogram, which correlated with the clinical spasm (myogram taken from the masseter muscles shows that the jaws were not involved in this instance); (2) absence of alteration in the electroencephalogram during the seizure. *B*, after partial curarization. Spontaneous spasms no longer occurred, and only mild contractions were induced, as illustrated by the brief burst of muscle potentials at the arrow in response to pinprick. Note lack of change in the basic pattern of the electroencephalogram after administration of curare. This response is typical of the five patients who were given tubocurarine chloride during recording of the electroencephalograms and electromyograms.

The red blood cell count was 4,120,000; the hemoglobin, 11.5 gm. per 100 cc. The white blood cell count was 3,700, with 64% neutrophiles and 36% lymphocytes. The urine was normal. The spinal fluid was under a pressure of 180 mm. of water and contained 1 lymphocyte per cubic millimeter and 22 mg. of total protein per 100 cc.

Immediately after admission the patient was taken to the electroencephalographic laboratory, where a team awaited, including an anesthetist with equipment for intubation and artificial respiration. An intravenous drip of isotonic sodium chloride solution had been started. Electrodes for the electroencephalographic study were applied in the usual positions; in addition, electromyographic recordings were made from the masseter, paravertebral, and abdominal muscles. With these initial preparations, spontaneous seizures, as well as seizures induced by noise and pinprick, were observed and correlated with the electroencephalogram and the electromyogram. During the seizures there was no appreciable change in the electroencephalogram. In the electromyogram bursts of muscle potentials, persisting as long as the clinical spasms, 15 to 30 seconds or more, were seen.

After the control period, tubocurarine chloride was administered intravenously through the drip tubing, at intervals of four minutes. A total of four injections were made. The first two were of 20 units (3.0 mg.) each, and the last two were 10 units (1.5 mg.) each, making a total of 60 units. In the observation period following each injection, there was a reduction in the severity and duration of spasms, which correlated with the reduction of voltage and duration of the muscle potentials. After the last injection there were no spontaneous seizures, and none could be induced for 60 minutes. The patient remained alert, and there were no significant changes in pulse, respiration, or blood pressure. While he was relaxed, 60,000 units of tetanus antitoxin was given intravenously, after a negative skin test.

Upon his return to his room, arrangements were made for constant bedside attendance. An additional 20,000 units of tetanus antitoxin was infiltrated around the site of the wound, and the area was then excised, with use of local anesthesia. A total of 300,000 units of procaine penicillin G was given daily through July 7. Tubocurarine chloride was administered at intervals of one to three hours intravenously in doses of 10 to 30 units, the amount depending upon the clinical status of the patient. At no time were muscle spasms or seizures allowed to return to their original severity. The most satisfactory periods of control were noted when the drug was given at hourly intervals in doses of 20 units. The patient remained afebrile during the entire period and was alert and able to cooperate in his treatment. Curarization was discontinued on July 7. He was released from the hospital, ambulatory and asymptomatic, on July 13.

The total dose of tubocurarine chloride U. S. P. was 2,246 units (336.9 mg.). The daily dose which most satisfactorily controlled his symptoms varied from 300 to 380 units. No signs of cumulative effects were seen in this subject.

Case 2.—A. D., a boy aged 8 years, was hospitalized on Feb. 21, 1952, because of "drawing in the face." On Feb. 8, while playing in a barnyard, he was struck with a stick beneath the right eye. A portion of a splinter of wood was removed; however, the wound did not heal and became infected. On Feb. 15 the mother noted that the face was pulled up and to the right. By Feb. 19 he had difficulty in speaking and swallowing and could not open his mouth completely, and the next day he was unable to eat or drink.

Examination revealed an apprehensive, irritable boy, who would, however, cooperate once his confidence was gained. The temperature was 101.4 F. (rectal); the pulse rate, 110 per minute, and the blood pressure, 115/70. There was an infected granulating area, surrounded by erythema and edema, on the face just below the right eye. The facial expression was typical of risus sardonicus. Intermittently the jaws would clamp shut and the face draw to the right. During periods of relative relaxation the jaws could be opened only 0.5 cm. Attempts to swallow fluids would cause him to choke, and the facial musculature and jaws would then go into severe spasm. During these seizures the head was drawn back and the abdomen became tight.

There were weakness of the right side of the face, including the brow, and inability to close the right eye completely. The skin was dry, hot, and inelastic. The stretch reflexes in the lower extremities were hyperactive, and there was patellar and ankle clonus. The remainder of the general physical and neurological examination was not remarkable.

The red blood cell count was 3,800,000; the hemoglobin was 11.0 gm. per 100 cc. The white blood cell count was 19,100, with 91% neutrophiles, 8% lymphocytes, and 1% monocytes. The urine was normal. The spinal fluid was under a pressure of 120 mm., contained no cells, and had a total protein content of 24 mg. per 100 cc.

On the evening of Feb. 21 the patient was taken to the operating room, where a general anesthetic was administered and a tracheotomy was performed. The area surrounding the wound

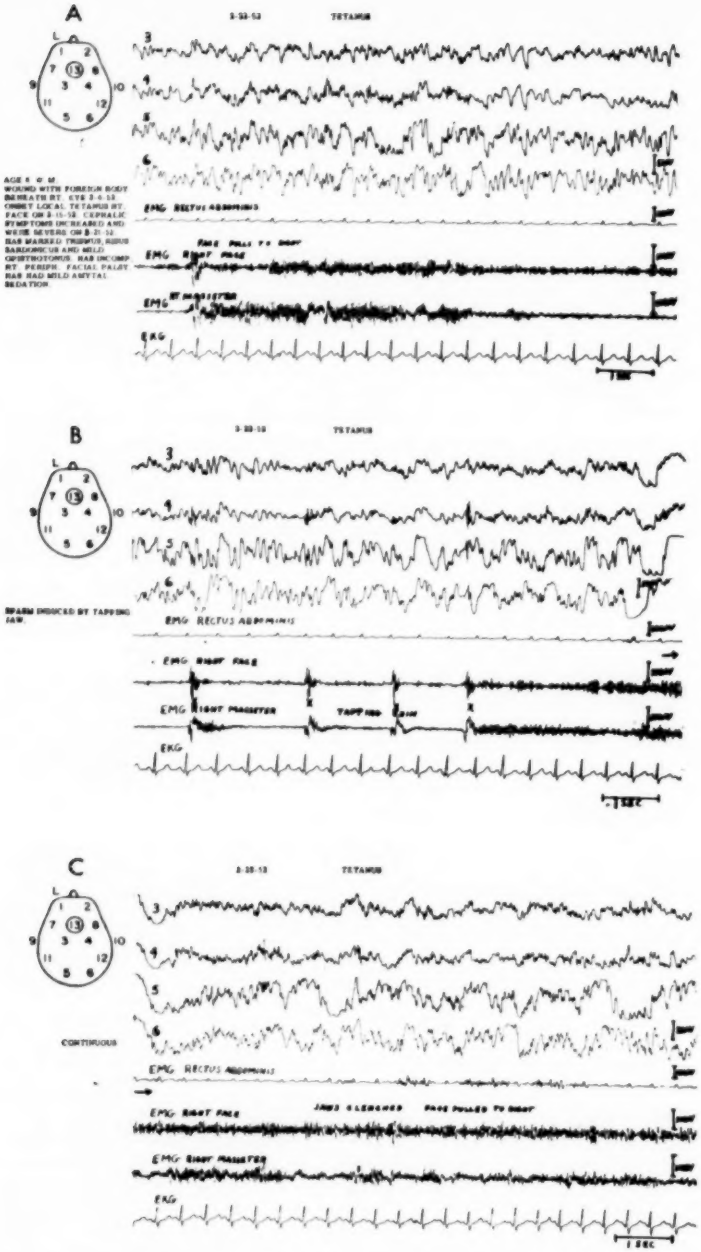

Fig. 3.—Electroencephalographic and electromyographic records from an 8-year-old boy with tetanus, showing "titration" procedure (Case 2). Onset of symptoms, seven days before, had followed a wound beneath the right eye. Moderate sedation had failed to alleviate the symptoms, and he had been allowed to awaken. (*A*) During spontaneous spasm, in which the jaws would clench and the face pull to the right, bursts of potentials are seen in the electromyogram from the right masseter and facial muscles. The electromyogram from the rectus abdominis shows no muscle potentials during the seizure, indicating that the truncal musculature was not involved. In this, and in subsequent, episodes no alteration is seen in the basic pattern of the electroencephalogram. (*B*) With each tap of the jaw, marked by X's, a jerk of the facial and masseter

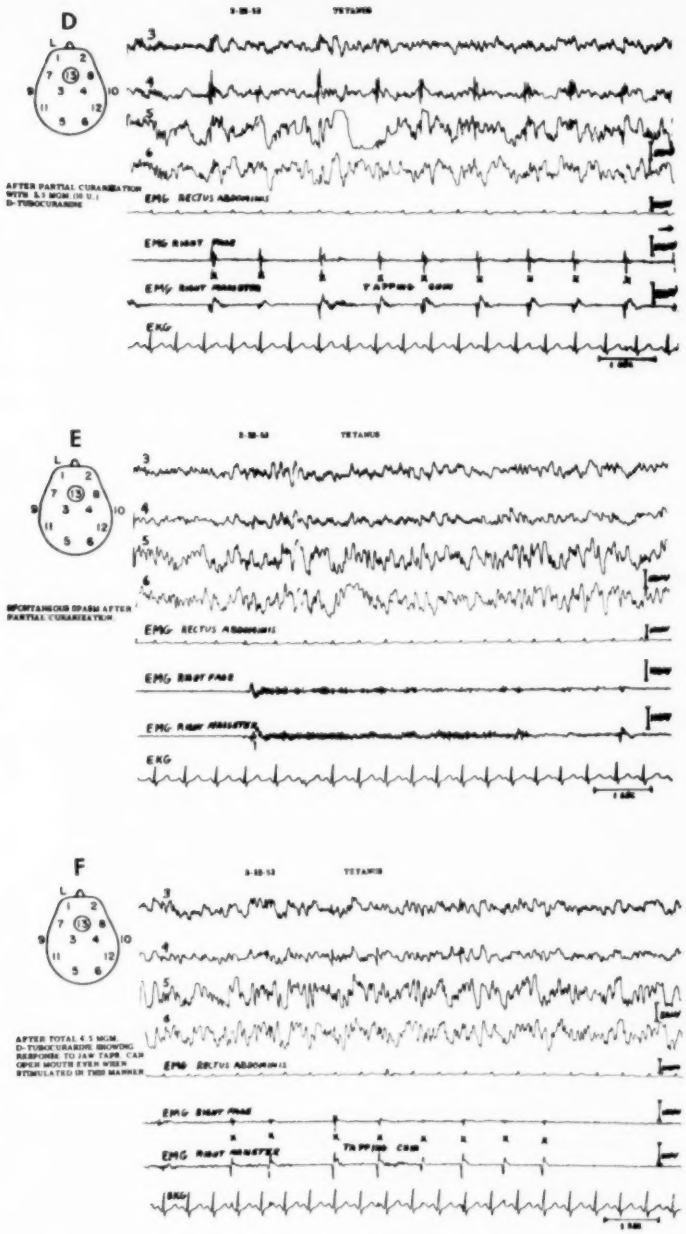

Figure 3 *Continued*

muscle occurred, and correlated with a brief burst of muscle potentials. (*C*) The record, during spasm induced by tapping, is continuous with *B*. (*D*) The response, both clinically and electrically, is reduced after administration of 10 units of tubocurarine chloride intravenously. (*E*) Milder spontaneous spasms still were seen after this partial curarization. Note reduction in voltage of the electromyogram. (*F*) After administration of a total of 30 units of tubocurarine chloride, tapping of the chin produced only slight response, and seizures no longer could be induced. There was no embarrassment of respiratory exchange and little effect upon voluntary muscular strength. This effect persisted beyond 60 minutes, and the patient was subsequently maintained on regular doses for a total of 14 days.

was infiltrated with 20,000 units of tetanus antitoxin and a block excision performed. A splinter of wood was found in the excised specimen. While he was under anesthesia, 40,000 units of tetanus antitoxin was given intramuscularly and 40,000 units intravenously.

During the night the patient had sedation with amobarbital (amytal®) sodium and paraldehyde, but the severity of the muscular spasms increased. All sedation was discontinued on the following morning in preparation for curarization. At 2:00 p. m. he was brought to the electroencephalography laboratory for "titration," as in the previous case (Fig. 3). A plastic cannula was inserted into an ankle vein to facilitate injections. During the control period spontaneous and induced seizures were observed and their effects correlated with the electroencephalogram and with the electromyograms taken from the masseter and facial muscles, at the angle of the mouth, and from the rectus abdominis. Spontaneous seizures, lasting up to 30 seconds, were observed. Tapping the chin lightly would produce a spasmodic jerk of the head, jaw, and face, corresponding with a brief burst of muscle potentials on the electromyogram. With repetitive tapping more prolonged spasms (10 to 30 seconds) were induced. No alterations were noted in the electroencephalogram during the seizures.

After this initial control period, tubocurarine chloride was injected intravenously in increments of 10 units and at intervals of five minutes, to a total of 30 units. After each injection there was diminution in the severity and duration of the spontaneous and induced spasms, which correlated with reduction in voltage and duration of the muscle potentials in the electromyogram. After the final injection the patient was able to open his mouth 2.5 cm. Seizures could no longer be induced. There were no changes in vital functions, and voluntary muscular strength remained good. This effect persisted beyond 60 minutes.

Curarization was continued from Feb. 22 through March 5. Initially 10 units was given intravenously every hour. This dose subsequently was increased to 14 units. The patient remained alert and cooperative through the entire course. An oral preparation of penicillin was administered by a tube which had been placed in the stomach for feeding. By the time of his release from the hospital, on March 15, there were no signs of tetanus. Mild right peripheral facial weakness persisted.

The total dose of tubocurarine chloride was 2,276 units (341.4 mg.). The most satisfactory control was obtained with the administration of 14 units intravenously at hourly intervals.

RESULTS

Six of the 13 patients with tetanus were treated by sedative medication, including administration of amobarbital sodium, phenobarbital sodium, paraldehyde, and tribromoethanol U. S. P. (avertin®) by various routes. In none of this group could sedation be given in sufficient amounts to abolish completely the spontaneous or induced tetanic myographic responses. Sedation was given at times to the point where respiration was severely embarrassed. When death occurred, it was associated with severe pulmonary congestion. In none of these patients was there any alteration in the electroencephalogram during the seizure of tetanus, whether the basic pattern was fast, slow, or dysrhythmic. This would seem to indicate that the tetanic seizures are not of cortical origin. Delta activity appeared only terminally or when the patient was under the influence of sedation.

Five of the 13 patients were originally given tubocurarine, by the method outlined above, to a point where spontaneous and induced seizures disappeared clinically and electromyographically for 40 to 60 minutes or more, without serious disturbance to the respiratory exchange or alteration in the electroencephalogram. The last two patients have been maintained successfully for periods of 10 and 14 days, respectively, on regular periodic administration of curare, with only enough sedation to allay anxiety and assure adequate rest. The sensorium remained clear throughout the course, and the patients were able to cooperate with the treatment. The usual maintenance dose varied from 10 to 20 units given optimally at hourly

intervals, and was continued as long as the patient gave any evidence of spontaneous or induced tetanic seizures. The other three patients originally curarized were treated subsequently with the usual sedative technique. All patients received tetanus antitoxin and antibiotic therapy in the form of penicillin.

SUMMARY

Simultaneous electroencephalographic and electromyographic studies are reported in 13 cases of tetanus, in 9 of which serial observations were made. Untreated patients showed no appreciable alterations in the electroencephalogram, even during the spasms. In the late stages, particularly if sedative therapy had been instituted, delta activity appeared. Patients treated with curare preparations to the point where spontaneous or induced spasms were made less severe or completely inhibited showed no changes in the electroencephalogram.

Two patients were treated exclusively with intravenous injections of tubocurarine chloride. A team was organized in cooperation with the department of anesthesiology to assure at all times an adequate airway and possible measures for artificial respiration. Tubocurarine chloride was administered in graded doses, up to 60 units in 40 minutes. As soon as the electromyogram showed no response to stimulation and there was no serious effect on respiratory exchange, the "titration" was considered complete. Subsequently, the patients were maintained on regular periodic doses sufficient to prevent seizures. This averaged from one-third to one-half the initial requirement, as determined by the "titration" procedure.

FAMILIAL OCULAR MYOPATHY AND EXTERNAL OPHTHALMOPLEGIA

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INVOLVEMENT of the oculomotor muscles in the course of a generalized muscular dystrophy is not common. Even more unusual is a dystrophy limited to the ocular muscles without evidence of muscular involvement elsewhere in the body. A few such cases have been described by Kiloh and Nevin.[1] We are reporting the clinical and pathologic observations on a patient who had this syndrome, and also the clinical findings in four members of his family. These cases form an entity, little recognized clinically, and in addition have a bearing on the subject of "chronic progressive nuclear ophthalmoplegia."

REPORT OF CASES

CASE 1.—A. X., a white man aged 68, had been well until about 20 years of age, when he noted the onset of slight ocular ptosis. This became worse slowly and progressively over the course of many years. Sometime after the onset of ptosis, slight external ophthalmoplegia occurred, which also was slowly progressive. Diplopia did not occur. The patient was otherwise well during this time. In 1922, at the age of 55, he fell off a chair and was unconscious for a period of less than a day, although the exact duration is not certain. He was taken to a hospital, where a fracture of the right femur was discovered. There was no fever. The neurologic status and the cerebrospinal fluid were said to have been normal. A diagnosis of epidemic encephalitis was made. Within a month after the accident the fracture healed, but the patient was seen to walk stiffly and had a coarse tremor of all extremities. He became depressed, with occasional crying, and would sit motionless for hours. He was retarded intellectually, but was taken care of by his family without too great effort. In 1932, at the age of 65, urinary incontinence occurred, his stiffness became worse, and his speech was more retarded. During the last two years of life he became gradually worse and was less able to care for himself. Two weeks before his admission to Montefiore Hospital, in June, 1935, he began to vomit and became stuporous.

The past medical history was not contributory, except for an attack of "brain fever" in childhood, with further details unknown. The family history was of interest, although there were no known oculomotor difficulties or ptosis in the family prior to the illness of the patient. He was one of five children, two males and three females, none of whom had any significant illnesses. The patient married a first cousin on the maternal side and had two sons, one of whom furnished most of the further details. This son stated that most of the members of the family had thick-boned and large skulls, as determined by roentgenograms, but none had hydrocephalus as far as was known. Further details of the family history are given in the reports of Cases 2 to 5 and in Figure 4.

From the Laboratory Division, Montefiore Hospital for Chronic Diseases, and Hartford Hospital, Hartford, Conn.

1. Kiloh, L. G., and Nevin, S.: Progressive Dystrophy of External Ocular Muscles (Ocular Myopathy), Brain **74**:115, 1951.

Physical examination on admission revealed a well-developed white man with a large head and an oily face. The heart and lungs were normal. The blood pressure was 130/80. Neurologic examination revealed fine, rhythmic tremor of all extremities, without motor weakness. Cogwheel rigidity was present in the upper extremities. The deep reflexes were all active and equal on the two sides, and there were no pathologic reflexes. Tests of coordination could not be carried out satisfactorily. Cranial nerve examination revealed pronounced bilateral ptosis (Fig. 1); small, slightly irregular pupils which reacted poorly to light, and eyes which could not be deviated in any direction. Sensory examination was unsatisfactory.

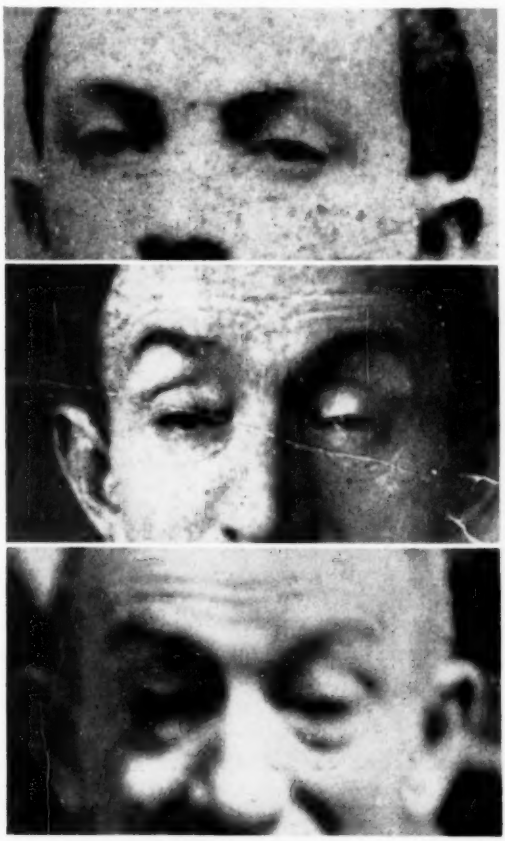

Fig. 1 (Case 1).—Unretouched photographs from the X. family album. They show the development of ptosis in the patient at the age of 16 (top), 60 (middle), and 68, shortly before death (bottom). Note the minimal degree of ptosis, especially in the left eye, at the age of 16, and the progression, with the characteristic wrinkling of the forehead, at the later ages.

Laboratory examination revealed that the blood sugar was 100 mg., urea nitrogen 36 mg., and creatinine 2 mg., per 100 cc. The Wassermann reaction of the blood was negative. The urine gave a 1+ reaction for albumin but was otherwise normal.

On July 14, 1935, the patient suddenly collapsed. The pulse was rapid; the lips were cyanotic; respirations were shallow, and a diagnosis of myocardial infarct was made. He died the next day.

Necropsy was limited to the cranial contents. The calvaria was heavier and thicker than normal. The brain weighed 1,430 gm. The floor of the third ventricle protruded as a cystic

mass the size of a walnut. The tuber cinereum and corpus callosum were stretched and thin. The lateral and third ventricles were dilated, and there was atrophy of the corpus striatum. The aqueduct was narrow and assumed a Y-shaped appearance, with almost complete approximation of the ependymal walls. The details of this finding are given in connection with Case 4 in another report.[2] The pallidal segment of the corpus striatum contained only a few large ganglion cells. Most of the cells of the substantia nigra were depigmented. The ganglion cells of the oculomotor and abducens nuclei were studied. Careful examination of these cells revealed them to be normal in number and appearance.

Study of sections of the eye itself revealed nothing of note. The eye muscles, however, were strikingly altered. There was partial replacement of muscle fibers by fatty tissue (Fig. 2). Throughout the remaining fibers there was a focal, but widespread, increase in sarcolemmal nuclei. Segments of muscle fibers with proliferation of sarcolemmal nuclei were found in

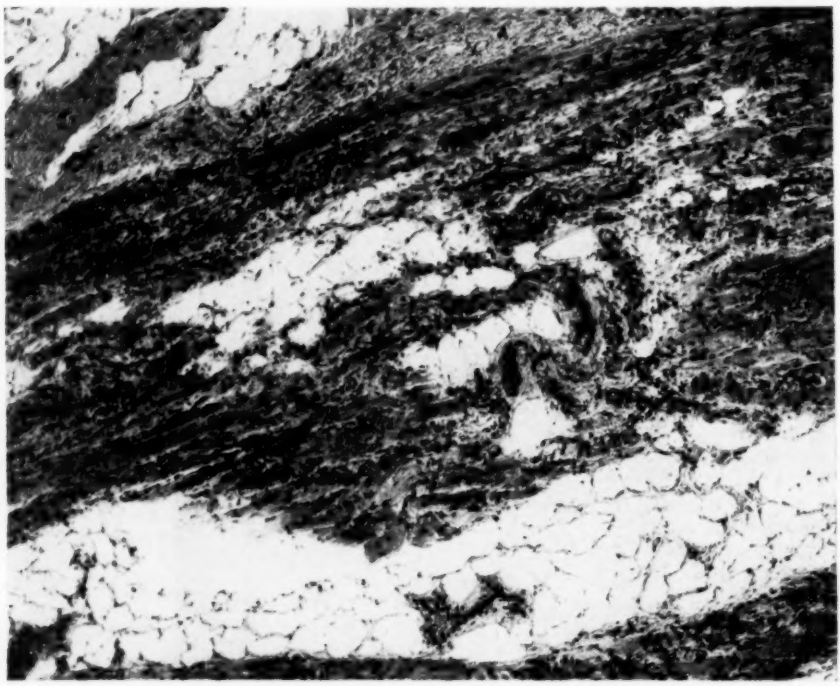

Fig. 2 (Case 1).—Photomicrograph (× 100) of lateral rectus muscle, showing fatty-tissue replacement of muscle fibers and focal proliferation of sarcolemmal nuclei. Hematoxylin-eosin stain.

fibers of otherwise normal appearance. Focal phagocytosis of some fibers was noted. Extensive loss of cross striations was also found, but with preservation of these structures in some fibers (Fig. 3).

There are three principal lesions in this case, each independent of the others. The pallidal and nigral lesions were those of the Parkinsonian syndrome. The aqueductal stenosis was a developmental alteration.[2] The lesions in the muscle were quite characteristic of a primary muscular dystrophy.

2. Beckett, R. S.; Netsky, M. G., and Zimmerman, H. M.: Developmental Stenosis of the Aqueduct of Sylvius, Am. J. Path. **26**:755, 1950.

Clinically, this patient, as well as some of his relatives, described below, had what has been called "chronic progressive nuclear ophthalmoplegia," although on clinical grounds alone the condition would be best described as "chronic progressive external ophthalmoplegia." The evidence against the nuclear origin of this syndrome is discussed in another section. To the best of our knowledge, this case is the only instance of such a disorder in which both the central nervous system and the oculomotor muscles have been studied.

CASE 2.—B. X., a man aged 54, was seen briefly in 1949 and again in 1952. He was the oldest son of the patient described in Case 1. Sometime in his teens he noticed ptosis and later weakness of movement of the eyes, both of which slowly and progressively became worse.

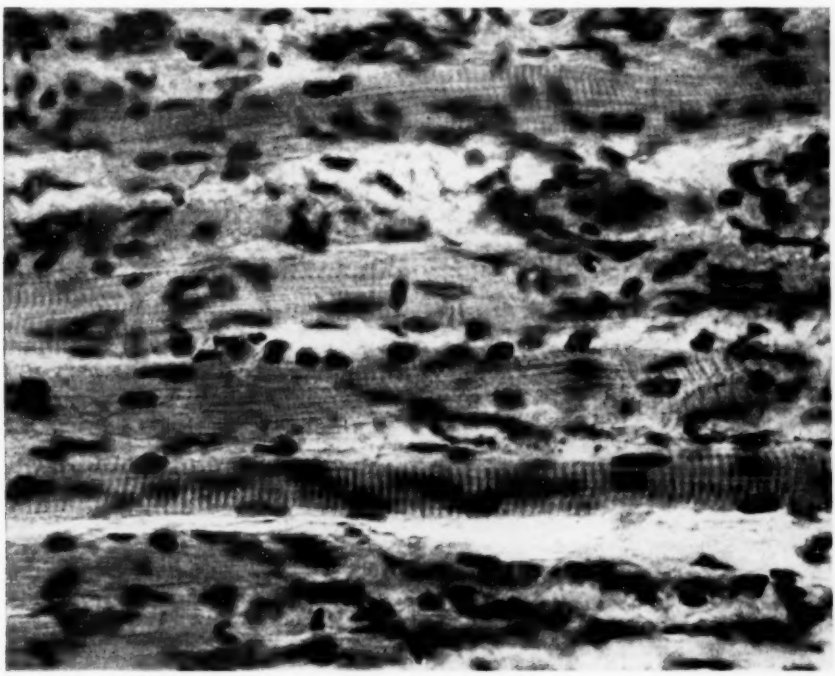

Fig. 3. (Case 1).—Photomicrograph at higher magnification (× 545), showing focal increase in sarcolemmal nuclei, some loss of cross striations, and destruction of portions of the fibers. Note that some fibers are normal. Hematoxylin-eosin stain.

Diplopia was not present at any time. He was otherwise in good health. After being examined in 1949, he took large doses of vitamin E for several months. Despite this, the ptosis continued to become worse.

Examination revealed a striking degree of bilateral ptosis with a compensatory backward tilt of the head and elevation of the frontalis muscle. These combined to give a characteristically sleepy appearance, similar to that of his father. When he was looking forward, the lids could be raised only to the midpupillary line with the most strenuous effort. Lateral, medial, and upward movements of the eyes were restricted symmetrically. Downward movement was normal individually and conjugately. Convergence was poor. Pupillary reactions to light, both direct and consensual, as well as the reactions on attempted convergence, were good. The fundi were normal. There were no other cranial nerve signs. Muscle power and tone throughout the body was normal, as were the deep reflexes.

A roentgenogram of the skull revealed normal optic foramens and a slightly thickened calvaria, but otherwise nothing abnormal.

A son and daughter of this patient (Case 2) were not examined. The son, aged 25, is said to have minimal ptosis, but the daughter is normal.

CASE 3.—C. X., a man aged 49, was the younger son of the patient described in Case 1. The history was similar to that of his brother (Case 2).

Examination revealed a slight degree of ptosis, slight limitation of lateral and upward gaze, but full movement downward. The ability to converge was poor. The pupils were round and equal, with good response to light and on attempted convergence. With fatigue the ptosis and limitations of eye movements became worse, but were never as striking as in the father or older brother. A roentgenogram of the skull revealed a mild degree of thickening of the calvaria, without abnormalities in the optic foramens or elsewhere.

CASE 4.—D. X., a man aged 21, was a son of C. X. (Case 3). This young man had no symptoms. Examination in 1952 revealed only poor ability to converge, without impairment of eye movements in other directions. The pupils were normal in size, shape, and reaction to light. Whether this inability to converge was indicative of a mild myopathy or represented another type of congenital defect cannot be determined at this time.

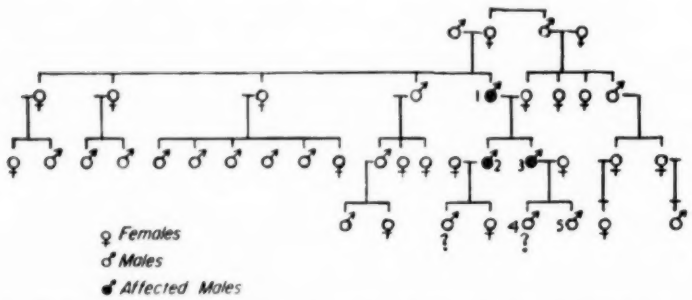

Fig. 4.—Pedigree of the X. family. The numbered patients were examined personally and are described in the text. The question marks indicate the two young patients who have signs which probably are indicative of the disorder. Note that Patient 1 married a first cousin.

A roentgenogram of the skull revealed only the mild degree of thickening of the calvaria seen in other members of the family.

CASE 5.—E. X., a youth aged 17, was the youngest son of C. X. (Case 3). There was neither a history of symptoms nor signs on examination.

The family tree is shown in Figure 4. Only members 1 to 5 were examined by us. The absence of ptosis or other signs in the rest of the pedigree was indicated by the history only. The disease has been seen with certainty in two generations, and there are perhaps minimal signs of involvement of the third generation. Females have never been affected, and apparently the transmission is by males.

COMMENT

Examination of the literature on external ophthalmoplegia and muscular dystrophy indicates that the definition and diagnosis of ocular myopathy is made partly by exclusion. There are many causes of external ophthalmoplegia, most of which can be distinguished readily from ocular myopathy. The causes may be grouped as neurogenic or myogenic.

Neurogenic Causes.—1. Ocular paralysis associated with increased intracranial pressure and intracerebral space-occupying lesions. It is to be expected that the diagnosis in this group will be made by competent neurologic and ophthalmologic examination.

2. Inflammations of the ocular group of cranial nerves.

3. Acquired diseases affecting cranial nerve nuclei, such as multiple sclerosis, syringomyelia, and amyotrophic lateral sclerosis (midbrain-pontine type). Evidence of more typical involvement elsewhere in the nervous system usually leads to the correct diagnosis in this and in the preceding group.

4. Aplasia of or congenital injury to the nuclei of the oculomotor, trochlear, and abducens nerves. Two necropsy reports of such "nuclear ophthalmoplegia" [3] are cited frequently. Both are concerned with patients in whom ophthalmoplegia appeared in adult life. The descriptions and illustrations of the alleged damage to ganglion cells are, in our opinion, dubious at best, and quite unconvincing. Damage to the axis-cylinders of the third, fourth, and sixth cranial nerves was not demonstrated. The external ocular muscles were not examined in these cases. Biopsy sections of eye muscles were made in one case in a third commonly cited report,[4] the findings being described as "atrophy of secondary type"; but these changes when studied carefully are more consistent with dystrophy than with secondary atrophy. This patient of Giardini's also had no symptoms until adult life. There is thus little support for the nuclear theory of external ophthalmoplegia (see Kiloh and Nevin [1] for an extended discussion).

Myogenic Causes.—According to Duke-Elder,[5] ophthalmoplegia may be classified according to the cause of the affection of the eye muscles.

A. General or systemic
   1. Myasthenia gravis, in which atrophy and lymphorrhages appear (ocular paralyses in as many as 50% of affected persons)
   2. Ophthalmoplegia due to involvement of the extrinsic muscles of the eye by dermatomyositis, amyloid disease, leukemia, lymphoma, or other neoplasms
   3. Exophthalmic ophthalmoplegia associated with thyroid disease, particularly with production of thyrotropic hormone of the anterior lobe of the pituitary [6]
   4. Chronic ophthalmic myositis secondary to tuberculosis, syphilis, trichinosis, and mycotic infections
   5. Ocular myopathy with systemic dystrophy [7]

B. Local
   1. Acute myositis of the ocular muscles as a result of orbital cellulitis
   2. Ocular myopathy without systemic involvement

3. Langdon, H. M., and Cadwalader, W. B.: Chronic Progressive External Ophthalmoplegia, Brain **51**:321, 1928. Jedlowski, P.: Sulla oftalmoplegia esterna nucleare cronica progressiva, Riv. oto-neuro-oftal. **20**:203, 1943.

4. Giardini, A.: Considerazioni su una forma "pura" di oftalmoplegia nucleare cronica progressiva, Riv. oto-neuro-oftal. **23**:181, 1948.

5. Duke-Elder, S.: Text-Book of Ophthalmology, Vol. 4: The Neurology of Vision, Motor and Optical Anomalies, St. Louis, C. V. Mosby Company, 1949.

6. Aird, R. B.: Experimental Exophthalmos and Associated Myopathy Induced by Thyrotropic Hormone, Ann. Int. Med. **15**:564, 1941.

7. Gartner, S., and Billet, E.: Progressive Muscular Dystrophy Involving the Extraocular Muscles, Arch. Ophth. **41**:334, 1949.

This grouping segregates muscle diseases that have either a distinct etiologic background or a direct association with a recognizable clinical syndrome. The changes seen in ocular muscles are diagnostic except those in myasthenia gravis [5] and exophthalmic ophthalmoplegia.[6]

THE EYE MUSCLES AND PROGRESSIVE MUSCULAR DYSTROPHY

The association of progressive muscular dystrophy involving the extrinsic muscles of the eye and voluntary muscle elsewhere in the body is established by the identity of the lesions in eye muscles with those in dystrophic muscles from other parts of the body. This observation was first made by Fuchs [9] and has been confirmed by others.[1] It is well known that muscular dystrophy may involve particular muscle groups selectively for long periods, and even for the entire natural course of the disease. The cases reported here exemplify this fact to an unusual degree. Ocular dystrophy may appear in persons with dystrophy of facial, nuchal, truncal, and distal muscles.[1] Ocular involvement is not common in dystrophy, but may even occur first. When it does occur, the order of involvement is not always the same. Both ocular and nonocular muscle dystrophies have a strong familial tendency. They also have in common a greater incidence at earlier ages, although persons up to the seventh decade of life may be affected. In the family reported here the disease is sex-linked, appearing in males, who transmit the disease to male offspring only. There is no evidence that the females transmit the disease, or that they are affected by it.

Beaumont,[10] Bradburne,[11] Faulkner,[12] Li,[13] Delord,[14] and Dutil [15] have described familial ptosis, usually associated with ophthalmoplegia, with occurrence in from two to five generations. Skeletal muscle function was not described, and muscle biopsies were not performed. In all, the authors collected data on 52 patients from family group totaling 112 members. Both males and females were affected in each family. Of the 52 persons affected, 23 were males and 29 were females. In the families reported by Bradburne and by Li the disease was congenital. In the other families the onset was at ages from 20 to 50.

This summary, unfortunately, does not provide any histologic data. It does indicate that a heredofamilial disease predominantly involving eye muscles and without evidence of involvement of the central nervous system occurs in succeeding generations. Since there were no biopsies, it may be that the congenital cases were

8. Brain, W. R., and Turnbull, H. M.: Exophthalmic Ophthalmoplegia, Quart. J. Med. **1**:293, 1938.

9. Fuchs, E.: Über isolierte doppelseitige ptosis, Arch. Ophth. **36**:234, 1890.

10. Beaumont, W. M.: Family Tendency to Ophthalmoplegia Externa, Tr. Ophth. Soc. U. Kingdom **20**:258, 1900.

11. Bradburne, A. A.: Hereditary Ophthalmoplegia in Five Generations, Tr. Ophth. Soc. U. Kingdom **32**:142, 1912.

12. Faulkner, S. H.: Ptosis with External Ophthalmoplegia Externa Starting in Adult Life, Brit. M. J. **2**:854, 1939.

13. Li, T. M.: Congenital Total Bilateral Ophthalmoplegia, Am. J. Ophth. **6**:816, 1923.

14. Delord, E.: Sur une forme de ptosis non congénital et héréditiare, Presse méd. **2**:592, 1903.

15. Dutil, A.: Note sur une forme de ptosis non congénital héréditaire, Progr. méd., Paris **16**:401, 1892.

not cases of true muscular dystrophy, although these cases presented the same clinical features as those in which symptoms appeared later in life.

A group of reports on biopsy specimens from patients with ptosis or ophthalmoplegia have been summarized by Kiloh and Nevin.[1] The first, by Fuchs,[9] described a histologic picture which was consistent with dystrophy, and the author, after considering a nuclear or a neuropathic etiology, concluded that the disease was myopathic. Subsequently, Silex [16] reported two cases of ocular dystrophy; Vollaro,[17] one case, and Sandifer,[18] one case. Of the five patients, four were females and one a male. At least one [18] had weakness of the orbicularis oculi, but in the others there was no evidence of other skeletal muscle involvement. Kiloh and Nevin [1] described another group of five patients seen by them. Four were males, and one was a female. There was no family history of ptosis, ophthalmoplegia, or muscular dystrophy. The patients apparently were not related. Evidence of involvement of extraocular and skeletal muscles was present in four of the five patients, although in one this consisted only of weakness of both orbicularis oculi. Biopsy specimens were secured from the orbicularis oculi, medial rectus, deltoid, superior rectus, and levator palpebrae superioris, a total of seven specimens from four patients. The characteristic changes of progressive muscular dystrophy were present. The authors thus showed that progressive muscular dystrophy may affect the external ocular muscles primarily or predominantly. That it affects muscle groups in a symmetrical fashion is consistent with its behavior elsewhere in the body.

The fact that this disease may involve the eye muscles alone does not establish this form as a separate nosologic entity. It does demonstrate how progressive muscular dystrophy may appear in the human body both widely and selectively.[19] Kiloh and Nevin [1] suggested that such cases be designated "progressive dystrophy of the external ocular muscles," or, in shortened form, "ocular myopathy."

HEREDITARY ASPECTS OF PROGRESSIVE MUSCULAR DYSTROPHY

Consideration of nonocular muscular dystrophy by Gates [20] discloses the following features:

1. About 60% of cases of progressive muscular dystrophy are sporadic; the remaining 40% occur in families.

2. Compilations of familial cases show a strong predominance in males, both in children (190:30) and in adults (127:25).

3. The mode of transmission varies. Families are cited in which the inheritance of progressive muscular dystrophy was of the following types: (*a*) recessive, sex-linked (male), but transmitted by females; (*b*) recessive, autosomal (not sex-linked); (*c*) dominant, low penetrance; (*d*) dominant, high penetrance.

4. In some families the same muscle groups are affected in all persons, while in others a wide variety of muscle groups are involved.

16. Silex, P.: Über progressive Levatorlähmung, Arch. Augenh. **34**:20, 1896.

17. Vollaro, A. de L., cited by Kiloh and Nevin.[1]

18. Sandifer, P. H.: Chronic Progressive Ophthalmoplegia of Myopathic Origin, J. Neurol., Neurosurg. & Psychiat. **9**:81, 1946.

19. Nothacker, W. G., and Netsky, M. G.: Myocardial Lesions in Progressive Muscular Dystrophy, Arch. Path. **50**:578, 1950.

20. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946.

In general, both sexes may be involved in families with ophthalmoplegia. Fiorenza [21] cited the cases of three brothers, all with ptosis, and one with ophthalmoplegia, but without mention of other affected relatives. Our attention was attracted to the exclusive incidence of the disease in the males of the X. family and the transmission by males. This phenomenon suggests sex-linkage of the responsible gene, other than linkage to the X chromosome. The problem may be represented by one of two alternatives. The first is that the gene responsible for hereditary ocular myopathy in this family is attached to the Y chromosome. If this is the case, the malady is expected to appear as a dominant for males; i. e., an afflicted male will transmit the disease to all his sons. His daughters will neither be affected by the disease nor be carriers of it. If all the male progeny are not affected, the gene may still be Y-linked, but of low penetration.

The second possibility is that the factor for ocular myopathy in this family is an incompletely sex-linked gene and that it behaves in the manner described by Haldane,[22] i. e., as an autosomal gene, except that the family in question produces an excess of affected members of one sex. Signs and symptoms attributable to ocular dystrophy have appeared in four of six male members of this family. Two younger male members may have the disorder, and one has no signs at 17 years of age. The six males represent three successive generations. The two unaffected males have not reached the age at which symptoms and signs appear in this family. It would be of genetic interest to observe this family further. Only six definite and five partially established Y-linked factors and six incompletely sex-linked factors have been described in human beings.[20]

SUMMARY

A form of muscular dystrophy limited to external ocular muscles was observed in two successive generations, and probably in a third. Only males were affected, and transmission was apparently through males. The diagnosis was established in the first affected male by necropsy. After consideration of reported cases of "chronic progressive nuclear ophthalmoplegia," it is concluded that these are probably cases of ocular myopathy. The present case is the first reported instance of this syndrome in which both the central nervous system and the ocular muscles were examined at necropsy. The lesions in the ocular muscles are comparable to those found systemically in progressive muscular dystrophy. Ocular myopathy, therefore, should not be considered as a nosologic entity, but only as a variant in the localization of the dystrophic process.

21. Fiorenza, I.: Contributo alla conoscenza dell'oftalmoplegia nucleare congenita a tipo familiare, Pediatria **29**:200, 1921.

22. Haldane, J. B. S.: A Search for Incomplete Sex Linkage in Man, Ann. Eugenics **7**:28, 1936.

EPILEPSIA CURSIVA

Syndrome of Running Fits

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ALTHOUGH the term epilepsia cursiva may be found in medical dictionaries, it is rarely mentioned in textbooks or in the medical literature. Running fits in dogs, caused by a diet of agenized flour (flour treated with nitrogen trichloride [agene®]) have been thoroughly studied by Mellanby,[1] Silver and associates,[2] and others.[3] Similar diets do not produce epileptic manifestations in man. Perusal of the literature reveals no previous psychiatric or electroencephalographic study of a group of patients with this type of epilepsy.

We have defined a running fit as an episodic alteration of awareness associated with running. Consciousness may be clouded to a variable degree. The activity may be coordinated but is inappropriate to the reality situation. A running fit is thus a type of automatism, and the syndrome is included in the ill-defined group of psychomotor epilepsies.

Nine cases have been studied intensively. In each instance the patient and one or both parents were interviewed in order to obtain detailed information concerning the emotional make-up, life situations, and their relationship to the disease. An attempt was made to determine the presence of any common emotional or physiologic factors which might have been of significance in precipitating the syndrome.

Three brief representative case summaries follow.

From the Sections of Neurology and Electroencephalography, University of Louisville School of Medicine, and the Louisville General Hospital.

1. Mellanby, E.: Diet and Canine Hysteria: Experimental Production by Treated Flour, Brit. M. J. **2**:885-887 (Dec. 14) 1946.

2. Silver, M. L.; Johnson, R. E.; Kark, R. M.; Klein, J. R.; Monahan, E. P., and Zevin, S. S.: White Bread and Epilepsy in Animals, J. A. M. A. **135**:757-760 (Nov. 22) 1947. Silver, M. L.; Zevin, S. S.; Kark, R. M., and Johnson, R. E.: Canine Epilepsy Caused by Flour Bleached with Nitrogen Trichloride (Agene®): Experimental Method, Proc. Soc. Exper. Biol. & Med. **66**:408-409 (Nov.) 1947.

3. Newell, G. W.; Erickson, T. C.; Gilson, W. E.; Gershoff, L. N., and Elvehjem, C. A.: Role of "Agenized" Flour in the Production of Running Fits, J. A. M. A. **135**:760-763 (Nov. 22) 1947.

REPORT OF CASES

CASE 1.—A. K., a single man now 21, had onset of his running fits at the age of 16. Their frequency varied from one a day to one a week. He had always been a shy, passive, inadequate boy, but had had no significant previous illnesses and was doing well in his third year in high school at the time of onset of the seizures. Shortly before his first spell he had an appendectomy, for which he was not adequately prepared emotionally. He awoke from the anesthesia prior to the completion of the operation and was terrified. The first seizure occurred a few days later. The usual aura was a feeling that people were drifting away from him; he then would become intensely fearful and run out of the house crying, "You ain't going to operate on me; I'll die first." When restrained, he became very combative. The episodes lasted only a few minutes, but no efforts of his parents could terminate them. After each fit he was stuporous for half an hour and then drowsy for an hour. He could recall fragments of the episodes, name some of the people whom he had seen, and remember an unreal feeling, a fear that he would be touched, and a need to "get away." Although he had always been inadequate as a child, this characteristic increased with the onset of the spells, and there were a gradual withdrawal from social contacts and an apathetic attitude toward work.

When seen at the age of 19, three years after the onset of his fits, general physical and neurological findings were normal. The electroencephalogram (Figure, *C*) was diffusely dysrhythmic and showed temporal spikes.

He was placed on treatment with 3 gm. of diphenylhydantoin sodium and 0.1 gm. of phenobarbital sodium a day. This medication was gradually increased over the subsequent year, during which time the spells decreased in frequency. He is now receiving 0.5 gm. of diphenylhydantoin sodium and 0.1 gm. of phenobarbital sodium daily. During therapy the episodes changed in character; the running component decreased, and the fits became merely brief spells of confusion with, at times, combativeness. He had a convulsion in November, 1951, but no other seizures since.

The nature of epilepsy was explained to the patient. He was reassured regarding the efficacy of antiepileptic drugs in controlling his seizures. Now the patient has gained a measure of confidence and is making a better work and social adjustment.

CASE 2.—L. T., a bright 7-year-old girl, had always been hyperactive and angered easily. Her father is a tense, anxious person, and her mother is placid and unemotional. Both parents preferred a more attractive sister, two years the patient's junior. From the age of 6 months to 6 years the patient had two or three grand mal seizures yearly. Neither parent paid much attention to these and sought no medical aid.

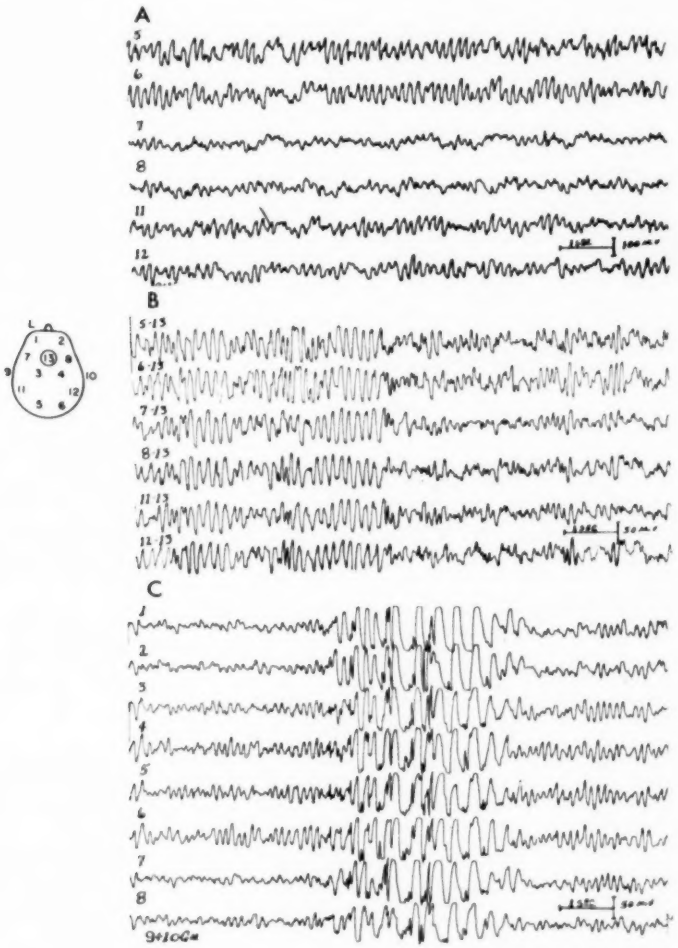
On one occasion, when the patient was 6 years of age, the sister tripped, fell, and was slightly injured. As the parents comforted her, the patient began to scream, fell to the floor, and became tonic. Similar episodes occurred five to six times daily in the following week, and the patient was admitted to the hospital. No spells occurred there, but immediately on her returning home there was a recurrence, the episode of falling now being followed by aimless running, which, however, was always away from the parents. These would end with her falling to the ground exhausted, or whenever the parents would catch her. On her readmission to the hospital the fits were controlled with barbiturates but could be reproduced by the patient at will. She was able to recall each entire episode and that she felt angry with her parents during them. Neurological examination gave normal results. The electroencephalogram was mildly dysrhythmic (Figure, *A*).

She was given phenobarbital and diphenylhydantoin medication, and the parents and child were reassured that the spells could be controlled. An explanation was given the parents of her need for attention and recognition. No grand mal seizures or running fits have occurred for 16 months, and she is less irritable and is able to direct her energy more constructively.

CASE 3.—L. C. is a very intelligent, confident, mature girl, now 12 years of age. When she was 3 years old, her father left to enter the Army; he was killed when she was 6, and her mother remarried when she was 8. She was very attached to her stepfather, almost to the exclusion of her mother. The patient had three episodes in 1951, as follows:

1. February: She arose one night, ran to the front door, and pounded on it, asking to be let in. This lasted three or four minutes, after which she realized where she was and returned to bed, with no subsequent recollection of the episode.

2. September: At night there occurred an episode of acute fear with confused talking for about one hour. This included statements such as "I am on the draft board, and I'm here to get you." There was amnesia for this.



Electroencephalograms of three patients with running fits. The range of abnormalities varies from mildly dysrhythmic activity (*A*) to pronounced spike-wave discharges (*C*).

3. September (a few nights later): The patient awoke, went outdoors, and ran down the street several blocks. She knocked at the doors and windows of a girl friend's house until finally the episode ended and she was returned home fearful and weeping. The next day there remained a vague recollection of running down the street and the great need to find a home and get inside.

Neurological examination gave normal results. The electroencephalogram was moderately dysrhythmic (Figure, *B*). The nature of the illness was explained to the patient and her parents, and she was placed on phenobarbital and diphenylhydantoin medication. There have been no further spells now for eight months.

RESULTS AND COMMENT

Table 1 shows the age and sex of each of the nine patients, the age at onset of their running fits, and the type and age at onset of other epileptic phenomena. All patients had, in addition to the running fits, grand mal and/or psychomotor seizures. In two patients the latter consisted only of episodic upper abdominal pain,

TABLE 1.—*Age of Onset, Electroencephalographic Findings, and Other Epileptic Phenomena in Cases of Running Fits*

Name	Age, Yr.	Sex	Age at Onset of Running Fits, Yr.	Other Epileptic Phenomena	Age at Onset of Epileptic Seizures	EEG	
						Dysrhythmia	Temporal Spikes
W. K.	10	M	8	Grand mal (?) psychomotor (episodic abdominal pain with confusion)	9 mo. 4 yr.	++	+
S. P.	7	F	6	Grand mal (?) psychomotor (episodic abdominal pain)	2½ yr. 2½ yr.	++	+
L. C.	12	F	11	Psychomotor (fear with confusion lasting 1 hr.)	11½ yr. (1 only)	++	+
A. K.	21	M	16	Psychomotor (episodic confusion with laughing and crying)	20 yr.	++++	+
F. G.	26	M	24	Grand mal	24 yr. (2 only)	+++	+
B. A.	9	F	6	? psychomotor (episodic abdominal pain) Atonic (episodic unconsciousness with falling)	5 yr. 6 yr.	+++	+
S. G.	8	M	5	Grand mal	5 yr.	+++	+
L. T.	7	F	6	Grand mal	6 mo.	+	+
B. S. W.	10	F	7	Grand mal	9 yr. (1 only)	+++	+
Summary	7-26 yr.	5 F; 4 M	5-24	Grand mal, 4; Psychomotor, 2; Grand mal and psychomotor, 3	Before RF,* 4; after RF, 3; same time as RF, 2	All have temporal spikes and dysrhythmia + to dysrhythmia ++++	

* RF indicates running fit.

and it was not possible to be certain that this was an epileptic manifestation. All had dysrhythmic electroencephalograms with temporal spikes. The Figure shows three illustrative tracings.

In two cases the running fits would occur during both the sleeping and the waking state; in three they occurred only at night, when the patient was asleep, and in four, only during the daytime. Their duration, as estimated by the patient and parents, varied from a few seconds to 10 minutes. Thus, no fugue states of many hours' or days' duration, with traveling of great distances, were noted. In two instances running fits occurred immediately after grand mal seizures. In three there was no aura; in two a vague fear was experienced prior to the seizure, and in two there was an aura of abdominal pain. From the patient's activity during the episode it appeared that all the patients were to some extent aware of their environment, but this awareness varied in degree. It was unusual for the patient to bump

into objects during the fit. Only one, L. T., could recall clearly the events of the seizure. Two had no recollection of the fit; three could recall having had a spell of some sort but none of the content, and three could recall the content vaguely.

Table 2 demonstrates the extreme variability of the personalities of the patients. Seven had a history, preceding the onset of running fits, of serious conflicts involving his or her relationship to the other members of the family. An acute trauma increased the conflict immediately prior to the onset of the running fits in most instances. For the patient with overprotective parents this consisted of starting school; for the man who was overdependent on his wife it was the birth of his first

TABLE 2.—*Personality Disturbances, Conflicts, and Precipitating Factors in Cases of Running Fits*

Name; Age; Sex	Personality	Conflict	Precipitating Factor	Behavior Problem
W. K. 10 M	Shy, placid	Unknown	Younger sister entered same grade at school	Episodic anger with destructiveness
S. P. 7 F	Intelligent +, sociable	Overprotective parents	Starting school	Breath-holding spells, destructive tantrums
L. C. 12 F	Intelligent +++, confident, mature	Strong attachment to stepfather	Unknown	None
A. K. 21 M	Unattractive, shy, inadequate	Personal inadequacy	Fearful surgical episode	Anxious, seclusive
F. G. 26 M	Introspective, dependent	Work frustration; overdependency on wife	Birth of first child	Episodic anger
B. A. 9 F	Unemotional, rigid	Hostility to rigid mother after father's desertion	Threat of loss of grandmother	None
S. G. 8 M	Intelligent +, rebellious	Hostility to alcoholic father	Father's loss of job	Episodic belligerance
L. T. 7 F	Intelligent ++, hyperactive	Rivalry with younger sister	Parental concern over injury to sister	Anxious, weeps easily
B. S. W. 10 F	Calm, affectionate	Overprotective father	Unknown	None
Summary	Variable	Variable Conflicts involving relationships with family, 7; inadequate, 1; unknown, 1	Some trauma that acutely increased the conflict, 7; unknown, 2	No change with onset of running fits, 1; no problem, 3; chronic anxiety, 2; episodic aggressive outbursts, 4

child; for the boy who had long-standing hostility to an alcoholic father it was the father's loss of his job. In the case of L. T. (Case 2), the parental concern over her sister's injury acutely intensified her rivalry with this sister, with its attendant guilt. In seven cases there was, at the time the patient was seen and therapy begun, an attitude or mode of reaction which might be called a "behavior problem." In each case this problem had existed for as long as the patient or other informants could remember, and there was no indication that this behavior had changed with the onset of the running fits or that any new behavior problems developed at this time.

Table 3 shows the subsequent course of this behavior problem after therapy and the effects of treatment on the seizures. If any change in behavior occurred, it was consistently toward improvement.

In six patients the running fits were controlled; in two the results cannot be determined, as there has been an insufficient period of observation since treatment

was instituted; in the remaining patient there was a marked decrease in frequency of the fits. Similar satisfactory control of other epileptic phenomena was obtained. Any change in behavior which occurred with therapy was consistently toward improvement.

All patients received phenobarbital and diphenylhydantoin medication and superficial psychotherapy of a reassuring type. The aim was to give the patient an understanding of his illness, explain the object of therapy, and give positive advice where

TABLE 3.—*Therapeutic Results in Running Fits*

Name; Age, Yr.; Sex	Frequency of Running Fits	Therapeutic Result*	Frequency of Other Epileptic Phenomena†	Therapeutic Result	Behavior Change
W. K. 10 M	2 per wk.	1 per mo.	GM status Psy, 1 per mo.	1 per mo. (abdominal pain)	None
S. P. 7 F	5 per day	None, 6 mo.	GM, 1 per mo. Psy, 1 per day	None, 6 mo. None, 6 mo.	Worse for 2 wk., then much improved
L. C. 12 F	2 only, 6 mo. apart	None, 8 mo.	Psy, 1 only	None, 8 mo.	None (no problem)
A. K. 21 M	1 per day to 1 per week	Decrease over 1½ yr. None, 8 mo.	Psy, 1 per wk.	None, 4 mo.	More confidence
F. G. 26 M	3 only, 1 yr. apart	None, 8 mo.	GM, 3 only, preceding each running fit	None, 8 mo.	None
B. A. 9 F	4 per day	None, 28 mo.	Psy, 1 a day Atonic, 3-4 daily	1 per day (abdominal pain) None, 28 mo.	None (no problem)
S. G. 8 M	2 per mo.	None, 4 mo.	GM, preceding running fits, 1 per mo.	None, 4 mo.	Worse for two mo., then improved; occasional nocturnal fear
L. T. 7 F	7 per day	None, 16 mo.	GM, 2-3 per yr.	None, 12 mo.	Less anxious; directs energy better
B. S. W. 10 F	3 per yr.	None, 17 mo.	GM, 1 only	None, 17 mo.	Anxious and tearful for 6 mo., then no problem
Summary	Two only, 1; three only, 1; several daily, 3; less frequently, up to 3 a year, 4	Controlled (no spells 4-28 mo.), 6; insufficient period of observation, 2; Decrease from 2 a wk. to 1 a mo., 1	Psychomotor, 5: 1 a day to 1 a mo., 4; one only, 1 Grand mal, 7; one only, 1; 2 a mo. to 1 a year, 6	Controlled (no spells 4-17 mo.), 4; one only, 2; insufficient observation, 1; psy unchanged, 2	No problem before therapy, 3: no change, 2; anxious 6 mo., then normal, 1 Problem, 6: much improved, 4; unchanged, 2; none finally worse

* All the patients received diphenylhydantoin (dilantin®) and phenobarbital.
† GM indicates grand mal; psy, psychomotor equivalents.

indicated. Actually, more psychotherapy was directed to the parents than to the patients.

All the patients studied were epileptic, since all had seizures other than the running fits, as well as electroencephalographic evidence of cerebral dysrhythmia. The electroencephalograms did not differ from those of the majority of persons with psychomotor epilepsy. It therefore seems possible that the running behavior was related to their interpersonal relationships and probably had a psychogenic component. One might explain the nature of this episodic behavior, if not its occurrence, in psychodynamic terms. It might be considered to be an "acting out" by the patient of his need to run toward (centripetal) or away from (centrifugal) a significant person or situation.

SUMMARY

A "running fit," epilepsia cursiva, is here defined as an episodic alteration of consciousness associated with running.

A group of nine patients were studied who had grand mal and/or psychomotor epilepsy and who also had running fits.

All patients had dysrhythmic electroencephalograms with temporal spikes.

These patients were of heterogeneous personality types, and many had conflicts in relation to members of their family. The histories suggest that these conflicts acted as precipitating factors in the illness and that the running was an expression of the conflict.

Phenobarbital and diphenylhydantoin medication was used, combined with superficial psychotherapy of a reassuring and explanatory type. In almost all cases this treatment produced seizure control and decrease in behavior problems.

PROLONGED POSTECLAMPTIC APHASIA

Report of a Case

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A CASE OF posteclamptic aphasia of seven years' duration is reported. This is the longest survival period on record, and the case is the only one in which improvement beyond a vegetative level has been reported.

REPORT OF CASE

History.—W. G., a white woman aged 24, was admitted to the psychiatric division of the Illinois Neuropsychiatric Institute on April 10, 1950, for study and evaluation. She had been brought to the outpatient clinic for a routine check. Her present condition dated from the birth of her only child, seven years before. When she was seen in the fifth month of pregnancy the family physician noted considerable ankle edema. There were no other abnormal findings at that time; the blood pressure was 120/75, and the urine contained no albumin. A day or so before the baby's birth the patient began to have convulsions. There is no record of blood pressure readings at that time. She had 14 more convulsions after delivery, by forceps, and was in a coma for several days. When she came out of the coma, she apparently had some difficulty in recognizing familiar objects and persons and at first did not talk at all. A little later the difficulty of recognition seems to have cleared up, but considerable amnesia was noted. She began to talk a little, though "she used the wrong words." One month after the birth of the child she was transferred to a state hospital, where she remained for six months. The hospital summary states: "She is confused, misuses words, and has defects of memory and amnesia." No abnormal physical or neurological findings were reported at that time; the blood pressure was 125/60, and laboratory findings were normal except for the presence of albumin in the urine.

After her discharge from the state hospital the patient lived at home with her husband, child, and mother-in-law. The mother-in-law had the major responsibility for the household, the patient apparently assisting only in the more routine chores. At times considerable resentment seemed to flare up between the two women, with the patient wanting to assume the sole care of the child and the mother-in-law blaming her for her inadequacies.

On her admission to the Illinois Neuropsychiatric Institute, the physical condition was essentially normal. The blood pressure was 120/60, and there were no abnormal ophthalmological or neurological findings. The spinal fluid pressure and dynamics were normal; an x-ray of the skull and pneumoencephalogram showed a condition within normal limits, and the electroencephalogram was of normal pattern. All laboratory tests (blood, urine, and spinal fluid) gave normal findings.

The available history preceding the child's birth was not remarkable. Apparently, the patient was a bright girl, who did well in school and left after completion of three years of

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Dr. Bernard Block, Chicago, brought this case to our attention.

From the Department of Psychiatry, University of Illinois College of Medicine, and the Psychiatric Division, Illinois Neuropsychiatric Institute.

high school in order to be married. There was no family history of nervous or mental disease. The child, now 7 years old, is from all accounts a normal, healthy girl.

General Behavior.—The patient was a pleasant woman of 24, neat in appearance, with no apparent signs of illness. She adjusted quickly to the ward routine, was helpful, and was generally liked by the patients and nurses. She knew that she had difficulty with her speech, that she could not read or write, and said that she wanted "to get better, to learn again." She was always willing to be examined. Emotionally, she was somewhat labile, and occasionally depressed, even in tears; again, a few minutes later, she would laugh, make jokes, and ridicule herself and others. At times she appeared euphoric and evidenced considerable witzelsucht; at other times she seemed frustrated and depressed by her own failures and inadequacies. Now and again she voiced all sorts of complaints: Her head ached; her bowels did not move; she had a pain in her arm; her eyes were fatigued; people were laughing at her. But even as she complained, one could not but feel that she was not really suffering very much; no one complaint lasted for any length of time, and each was verbalized without much emotion.

Sensorium.—The patient was only partly oriented. She knew that she was in a hospital, but she did not know the name. She knew the season but not the exact date. She understood that she was talking with her physician, distinguished nurses and patients, etc. There was considerable memory impairment, most marked for the period of the acute illness seven years ago, but reaching in some instances into her childhood, at others into more recent events. She knew her birthday, Sept. 8, because she had been told about this date so often, but did not know the year. She knew neither the date of her marriage nor her child's birthday.

Peripheral Sensory and Motor Activities (Gross Examinations Only).—No notable motor defects of either power or precision had ever been elicited. Eyegrounds, visual acuity, color efficiency, and visual fields were all normal. Ocular pursuit movements were intact in all directions. There was no spontaneous nystagmus; rotation nystagmus was not tested. Visual flicker fusion, however, was markedly reduced, clearly beyond the normal limits. Auditory, tactile, and kinesthetic localization was normal. Weight discrimination was normal. There was no astereognosis or finger agnosia. There was no primary dysarthria.

Language Functions.—Spontaneous speech was on the whole very good; to the casual observer it might appear almost perfect. She occasionally searched for names of objects, persons, or activities. Her use of grammar was normal for the rural environment in which she lived. She did not speak in "telegram style." At times, there were mistakes in the use of the "small" words, especially pronouns and prepositions. Occasionally she produced substitutions of verbal paraphasic character, although this was infrequent. Still rarer were "mispronounciations" of the literal paraphasic type.

The patient's reactive speech was much poorer than her spontaneous speech. In fact, it was good only when she could give very brief answers to concrete questions. Otherwise, defects in memory, in the understanding of the several concomitant parts of a question, and in the naming of objects, persons, verbs, and adjectives came to the fore. There were frequent verbal paraphasic mistakes, and more rarely some literal paraphasia could be noted. There were some attempts at compensation by means of well-preserved speech automatisms and a degree of what might be called witzelsucht.

The patient did not appear to have any difficulty in recognition of familiar objects and pictures of familiar objects. When presented with a group of objects—or a picture with many objects—she immediately pointed to the one named by the examiner. Nor was there any difficulty in the use of such familiar objects as pencil, and scissors.

Naming of objects, on the other hand, was severely defective. It is somewhat better in spontaneous speech, and when the patient picked at random individual objects out of a group than when the examiner presented single objects to be named by the patient. Manipulation per se, however, did not seem to facilitate the finding of the name. A good deal of circumlocution, as well as verbal paraphasic substitution, could be observed as the patient tried to name objects.

Oral repetition of sentences, meaningful words, meaningless syllables, sounds, letters, and numbers showed no defect. Meaningful material was produced meaningfully, i. e., without "sound imitations." The only difficulties observed were on long sentences which contain many separate items. Here the usual telescoping appeared.

There was no primary difficulty in the initiation and speaking of familiar series. The alphabet, the number series through about 30, and the days of the week were produced correctly, the

patient starting and stopping without the examiner's aid. She had some difficulty with the months of the years, eventually went correctly through August, and then "loses track" of the rest.

There appeared to be no primary defect in the understanding of spoken language. She followed simple instructions with ease and apparently understood simple questions without difficulty. On the other hand, more complicated intructions or explanations which involved the simultaneous presentation of several factors seemed to present almost insurmountable obstacles to her.

The patient's reading consisted only of the recognition of individual words, primarily nouns, adjectives, and verbs. There was no reading of sentences, although she would occasionally read a "phrase"—a response similar to her spontaneous use of such automatic phrases. In her reading of single words a great many substitutions of the verbal paraphasic type occurred. There was also some real "guessing," of which she was perfectly conscious. In general, when she "substituted" she seemed satisfied with her performance; but when asked whether she was sure of the correctness of her productions, she usually said, "I don't know," or "you tell me." At times when she found herself unable to recognize a word, she started spelling the word, i. e., reading the single letters, more or less correctly. This procedure did not, however, help her in finding the word.

The patient could not read at all the "small" words, i. e., articles, pronouns, and even three-letter verbs and nouns. Here she invariably substituted some other "small" word, sometimes one of a similar letter configuration, sometimes in apparently random fashion, and occasionally she seemed to "hit" the correct word.

There was, however, some "incidental" reading. In the absence of any intention and/or instruction to read, the patient would read aloud, and quite often correctly, for instance, the labels on objects. In line with this was her relatively good performance when presented tachistoscopically with material to be read. Under such conditions she read nouns and verbs at least as well, if not better. At the same time, she did not read the "small" words or, if she attempted to do so, made the same mistakes as in extended presentation.

Reading of numbers was poor for all numbers containing more than one digit; it was reasonably good, though by no means normal, for one digit numbers. Again, there were substitutions, often by the number which followed the number presented in the series.

No difference has ever been observed between reading printed and handwritten material.

Writing.—The patient did not write, either spontaneously or on dictation, with the exception of the alphabet, the number series, and her own name. There were occasional malformations of letters. She wrote with her left hand. She had apparently always been left-handed.

Copying was generally poor and very laborious; but, given unlimited exposure time, the patient eventually copied single letters, words, numerals, and simple drawings. In her copying of letters and words, the unit of her procedure was not the letter, but the single stroke, which gave rise to occasional constructive malformations.

Written reproduction of tachistoscopically presented material was, on the other hand, surprisingly good. With exposures of 0.01 second, the patient occasionally reproduced a whole word correctly, at other times a number of letters—with or without malformations and with occasional "misspellings"; most striking of all, there were a number of correct productions of words which the patient either did not "read" aloud at all or for which she produced gross verbal paraphasic readings.

Numerals, Numbers, and Arithmetic.—The patient copied numerals without much difficulty and wrote single-digit numbers on dictation, with occasional "substitutions." The same held for recognition of one- and two-digit numbers and their reading aloud. She did not recognize the signs for the arithmetical operations; and even when told their names, she did not know what to do with them. Even after careful explanation, the patient never really understood the process of adding or subtracting and could not do so even with small, one-digit numbers.

The patient could count, i. e., reproduce the number series, which is what she did when presented with a number of objects and asked to count them. She usually lined up the objects in a row, then touched one after the other as she said the number series. Since she occasionally skipped a number in the series, she did not always, but did very often, end with the correct number. When prevented from lining up the objects and from touching them, the patient "nodded" at each as she repeated the number series, but she tended to get confused more easily

and success was rarer. She did not immediately recognize number patterns. She had to "count," and thus :·: was more difficult for her than. . . . . The reverse is true for normal subjects.

The patient could not "handle" money. She recognized single coins and gave their popular names, e. g., "dime," "nickel," "penny." The word "cent" was quite unfamiliar to her. Asked how many cents—or pennies—are in a dime, etc., she could not tell. It goes without saying that she could not "make change." Reading the clock was equally impossible. The patient could not tell the time that a clock was set to, nor could she set the clock to a time indicated. Even copying a clock setting was difficult, since she reversed the hands about half the time. She did not recognize standard clock equivalents, e. g., "lunch time," the "time to get up in the morning," etc.

Perceptuomotor Functions.—The patient performed approximately at an 8-year level on a variety of simple drawing tests. On more complicated drawings, including copying of drawings, she made real errors of construction.

Tests of Abstraction.—On the Goldstein Block Design test, the Weigl test and object-sorting tests the patient's performance was extremely "concrete." No learning was demonstrated. She did relatively well, on the other hand, with the color-sorting and stick tests.

The patient could not give similarities, differences, or opposites. She could not explain proverbs, homonyms, or absurd sentences. She had lost the concepts of left and right. She could not make comparisons between even simple objects or statements.

She did well, on the other hand, on Bourdon's test and the Heilbronner pictures. She quickly caught on to "rhyming" after demonstrations and when asked to give a word which rhymes with one presented by the examiner, she did this quite adequately. No apparent disturbance of body schema, finger gnosis, and simple directions as tested by Head's test, Goldstein's stick tests, etc., was revealed. Great difficulty, however, was had with the representation of imaginal directions, e. g., explaining or sketching the way from the ward to the yard, etc. On psychometric testing, she achieved an intelligence quotient of 50 on the Wechsler-Bellevue test.

Summary of Psychological Findings.—This patient shows a severe central aphasia seven years after eclampsia at childbirth. We found signs of considerable amnestic aphasia, acalculia, alexia, and agraphia, together with a severe defect of abstraction. There is also a pronounced amnesia, especially for events at the time of the acute illness. The examination of peripheral sensory and motor functions showed nothing abnormal, but there was a striking decrease in visual flicker fusion.

COMMENT

Prolonged sequelae of eclampsia at childbirth appear to be extremely rare. A review of the literature does not reveal a single case of similar duration. A number of cases with aphasia-like symptoms lasting for several weeks, or even a few months, apparently followed by complete recovery, are reported. More recently, Josephy and Hirsch [1] and Lowenberg and Lossman [2] published findings on two women who, having survived puerperal eclampsia, lived on a purely vegetative level until death, three months later in one case, and seven years later in the other. Our patient thus appears to be the only one on record who has shown improvement considerably beyond a vegetative level, yet far less than complete recovery, and who, with such partial recovery, has survived for so long a time. According to the pathological findings reported by Josephy and Hirsch and by Lowenberg and Lossman, the condition they found might well be characterized as a "decortication." In the case presented here we have psychological findings in agreement with such a hypothesis, but as yet (September, 1952) no physical findings to substantiate it.

1. Josephy, H., and Hirsch, E.: Eclampsia: Report of a Case in Which There Was Extensive Destruction of the Brain, Arch. Path. **42**:391, 1946.

2. Lowenberg, K., and Lossman, R. T.: Atrophy of the Brain Following Puerperal Eclampsia, Am. J. Path. **10**:697, 1943.

EFFECT OF DIMERCAPROL (BAL) IN HEPATOLENTICULAR DEGENERATION

Report of a Case, with Clinical and Electroencephalographic Study

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OBSERVATIONS on the development of Parkinsonian syndromes in persons exposed to toxic substances, in particular to heavy metals, have stimulated interesting investigations concerning the pathogenesis of these extrapyramidal diseases.

In cases of hepatolenticular degeneration, for example, an increased content of copper in the liver and brain tissues has been demonstrated.[1] Recently, also, an increased excretion of copper [2] and amino acids has been found in the urine of patients with this disease. Since it had been observed [2a] that dimercaprol U. S. P. increased the urinary output of copper in a patient with hepatolenticular degeneration, Cumings [3] administered dimercaprol to four patients with this disease. In three of these patients a significant clinical improvement occurred. Denny-Brown and Porter [4] have recently observed the beneficial effect of dimercaprol in five cases of the disease.

The purpose of this communication is to report the clinical and electroencephalographic observations made on an additional patient with hepatolenticular degeneration who was treated with dimercaprol.

REPORT OF CASE

History.—Mrs. H. O., aged 29, was admitted to the department of Neurology of this hospital in August, 1951, complaining of general weakness, headache, marked tremor of her extremities, and disturbance of gait.

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1. Haurowitz, F.: Über eine Anomalie des Kupferstoffwechsels, Ztschr. physiol. Chem. **190**:72, 1930. Glazebrook, A. J.: Wilson's Disease, Edinburgh M. J. **52**:83, 1945. Cumings, J. N.: Copper and Iron Content of Brain and Liver in the Normal and in Hepatolenticular Degeneration, Brain **71**:410, 1948.

2. (a) Mandelbrote, B. M.; Stanier, W. M.; Thompson, R. H. S., and Thruston, M. N.: Studies on Copper Metabolism in Demyelinating Diseases of the Central Nervous System, Brain **71**:212, 1948. (*b*) Porter, H.: Amino Acid Excretion in Degenerative Diseases of the Nervous System, J. Lab. & Clin. Med. **34**:1623, 1948.

3. Cumings, J. N.: Effects of BAL in Hepatolenticular Degeneration, Brain **74**:10, 1951.

4. Denny-Brown, D., and Porter, H.: Effect of BAL on Hepatolenticular Degeneration, New England J. Med. **245**:917, 1951.

Her symptoms had started four years previously, when, after the birth of her second child, she noticed unsteadiness in walking. A year later there appeared shaking of her left hand and, subsequently, of the right hand also. Slowing and slurring of speech were noted, and she began to be troubled by excessive lacrimation and salivation.

In June, 1951 (two months prior to admission), the patient had been admitted to another hospital because of attacks of severe vertigo and fainting spells, accompanied by vomiting. There, a roentgenogram of the skull and examination of the cerebrospinal fluid revealed no abnormality, and the patient was released without further clinical studies. In the following weeks her condition rapidly deteriorated. She noticed impairment of memory, and her speech became markedly slurred. With the increasing tremor of the extremities, the performance of skilled acts, such as writing and sewing, became impossible, and walking became difficult. The patient spent most of her time in bed. She experienced attacks of severe headache, accompanied by hypersalivation and excessive lacrimation.

Except for a tonsillectomy at the age of 10, her health record was clear. Menstruation began at the age of 13 and was regular until six years prior to admission, when there was beginning of polymenorrhea and hypermenorrhea. She had been married for 10 years and had given birth to two normal children.

Family History.—The patient's parents were not related, and there was no suggestion of nervous or hepatic disease in either family. Her father died at the age of 61, of periarteritis nodosa. Her mother, aged 56, from the age of 40 had had gall-bladder disease. The patient was the second of five children, three of whom died in their early years of neurological or hepatic diseases.

The eldest child died at the age of 18 of a chronic neurological disease which was considered to be "encephalitis." The third child died at the age of 22, of acute yellow atrophy of the liver. The fourth child was a healthy man, without any history or complaints referable to the liver or the nervous system. The results of clinical and neurological examinations were normal, as also were those of liver function tests and an electroencephalogram. The fifth child, a boy, died of acute liver disease at the age of 9½ years, after an illness that had lasted 48 hours.

Clinical and Laboratory Findings.—On admission, general physical examination disclosed a well-nourished woman with a reddish-purple complexion. The temperature, pulse, and respirations were normal. The blood pressure was 130 systolic and 80 diastolic. There was no eruption, jaundice, or venous engorgement. Varicose veins were found in both legs, especially in the left, where perimalleolar telangiectases and local edema were noted. The cardiovascular and respiratory systems were normal. The abdomen was soft, and the liver and spleen were not palpable. The liver dulness was within normal limits. There was no sign of ascites or evidence of collateral venous circulation. No enlarged glands could be palpated.

Neurological examination showed that all her movements were slow, as was her speech, which was somewhat slurred. The facies was slightly "fixed" and displayed a smiling appearance. Mentally and emotionally the patient was normal. The cranial nerves were normal. At rest, both hands displayed a slow, rhythmical tremor of small amplitude. With the arms outstretched, a coarse, rhythmical tremor of both hands became visible, periodically increasing in amplitude on the left side. Here it became a rhythmical extension-flexion movement of the wrist of three to four oscillations per second, constituting the *Flügelschlagen* (wing-beating) movement described by Strumpell. There was a slight increase of tone in the left extremities. Motor power was somewhat diminished in both legs and in the left arm. Deep reflexes were slightly increased in the left extremities. Babinski and Chaddock signs were elicited in the left leg. Abdominal skin reflexes were present and equal on the two sides. There were no sensory disturbances. The performances in the "finger-to-nose" and "heel-to-knee" tests were disturbed, more especially on the left side, as were alternating movements of the wrists. There was a marked intention tremor in the left arm. The gait was broad-based and insecure. When standing with her eyes closed, the patient swayed and finally fell to the left side.

Examination of the eyes revealed a Kayser-Fleischer ring of grayish-brown color, about 1.5 mm. in width. Eye movements were normal, and there was no nystagmus. Dark adaptation was reported to be greatly impaired. Lumbar puncture gave clear fluid under normal pressure, without any abnormal chemical or serological findings.

Laboratory examination showed 4,500,000 erythrocytes, 13 gm. of hemoglobin per 100 cc., and 7,500 leucocytes, with a normal differential count. There were 180,000 thrombocytes per cubic millimeter. The blood sedimentation rate was normal. Bleeding, clotting, and clot-retraction times were normal. The prothrombin time was found to be 42, 55, and 67% of normal, respectively, on three occasions. Determination of the thromboplastic activity of the plasma was performed on thrombocyte-prothrombin-free oxalated plasma by comparing the clotting times before and after shaking with glass powder and the addition of prothrombin-containing plasma. On comparison with a normal control run simultaneously, the thromboplastic activity of the plasma was found within normal range.[5]

Urinalysis revealed increased urobilinogen excretion (+ to +++ on several occasions) as the only abnormality. Urinary α-amino-nitrogen excretion was found to be 179.5 mg. in 24 hours. The urea clearance was normal. Microscopic stool examinations revealed nothing abnormal. Unfortunately, because of technical difficulties, no satisfactory copper estimations could be performed.

Chemical studies of the blood gave the following results: urea, 28 mg. per 100 cc.; fasting sugar, 98 mg. per 100 cc., with normal glucose tolerance; total protein, 7.9 gm., albumin, 4.1 gm., and globulin, 3.8 gm., per 100 cc.; total cholesterol, 284 mg. per 100 cc., with a free cholesterol-ester ratio of 1:2.3. The cephalin-cholesterol flocculation test and the Takata-Ara test gave negative results. Thymol turbidity measured 2 units, and Weltmann's coagulation band was 8. Dilution and cold-fraction tests, as well as the formol-gel test, gave negative reactions. The indirect van den Bergh reaction was + and the direct reaction ±. The hippuric acid and sulfobromophthalein tests gave normal results. Alkaline phosphatase was 5 units; phosphorus, 3.8 mg. calcium, 10.3 mg., and potassium, 22 mg., per 100 cc. The Wassermann-Kolmer and Kahn reactions of the blood were negative.

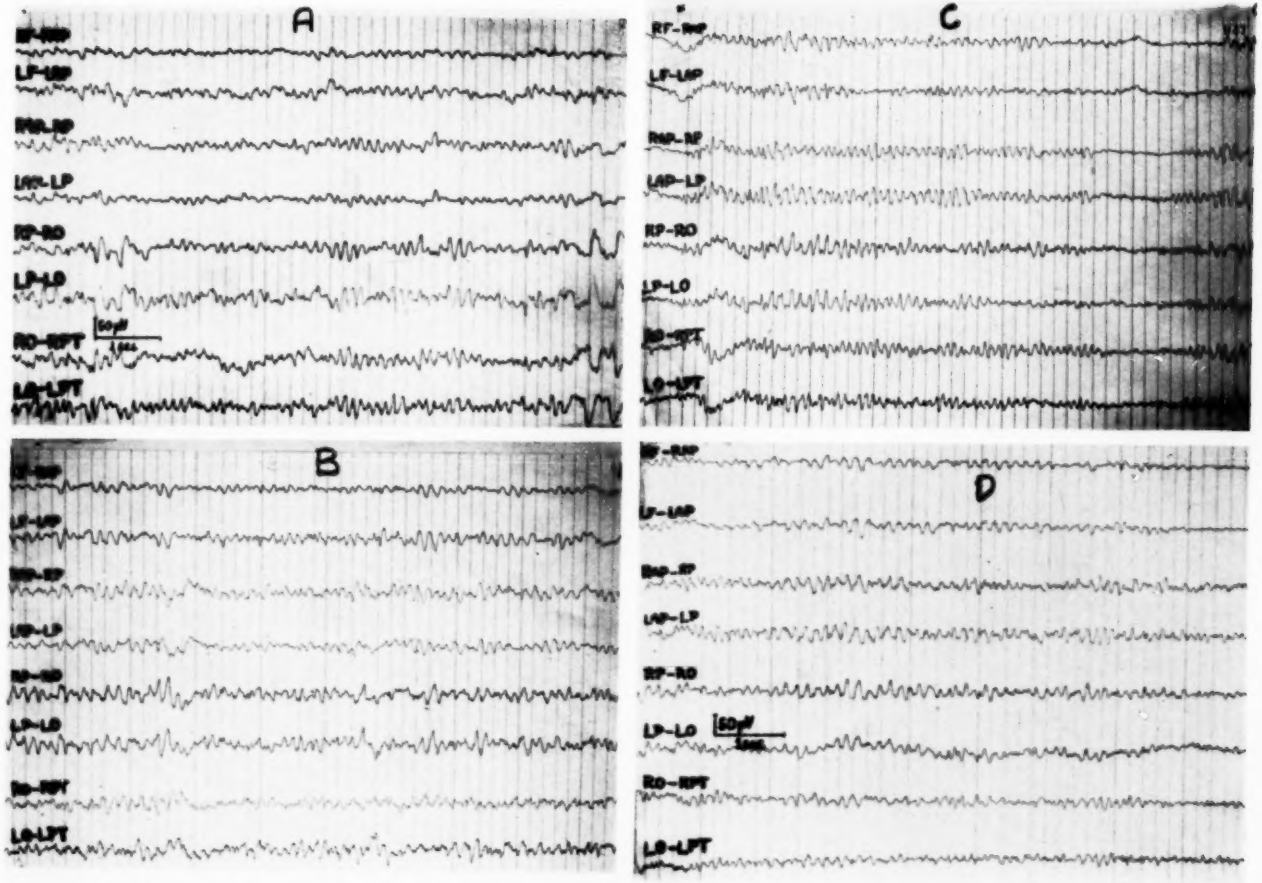
Electroencephalographic records obtained on three occasions showed a considerable degree of abnormality (Fig., *A*). The basic activity was alpha waves of 6½- to 8-cps frequency and 40 to 80 microvolts. This activity was fairly regular and symmetrical and showed a good "blocking" response. A considerable amount of diffuse, synchronous, and symmetrical slow activity was recorded from all leads, consisting of medium- to high-voltage (100 to 160 microvolt) waves of 5- to 3-cps frequency. The majority of the slow potentials were in the 5- to 4-cps (theta) range. In addition, rather frequent bursts of waves of 5- to 3-cps frequency, lasting 1½ to 2 seconds, were observed. Overbreathing for two minutes caused a considerable increase in the incidence of these bursts.

Effect of Dimercaprol on Clinical and Electroencephalographic Picture.—The diagnosis of hepatolenticular degeneration in this case was based on the presence, in a young person, of extrapyramidal and pyramidal signs, the *Flügelschlagen* and the Kayser-Fleischer ring, in association with evidence of hepatic insufficiency; and treatment with dimercaprol was decided upon. The first series of injections was started on Nov. 18, 1951. As recommended by Prof. R. H. S. Thompson,[3] a total of 2.2 gm. of dimercaprol was administered by intramuscular route, a 10% solution in peanut oil being used. The patient received two daily injections of 100 mg. each, i. e., 2.8 mg. per kilogram of body weight a day. In a period of six months four such courses were administered. The treatment was fairly well tolerated by the patient, who complained only of nausea, blurring of vision, and occasional vomiting.

Toward the end of the first course of treatment a considerable improvement in the patient's condition was observed. She became more active, and movements and speech became freer. The tremor, particularly the "wing beating," diminished considerably. The patient reported that she felt better and that her headache had become less severe. A second series of injections of dimercaprol was given after an interval of two weeks.

When the patient was seen again, at the end of January, 1952, further improvement in her condition was observed. Her speech was well articulated and fluent. She was able to walk around freely, although a slight rigidity was noticeable in her left leg. She told us that at home she had been able to care for herself, and even to do some housework. She had had no headaches or fainting spells.

5. Dr. A. de Vries, of the Laboratory of Clinical Investigation, made these determinations.



Electroencephalographic changes observed in the course of dimercaprol treatment. *A*, record taken on Aug. 28, 1951, before institution of treatment; *B*, record taken on Dec. 10, 1951, after first series of dimercaprol injections; *C*, record taken on Jan. 28, 1952, after second series of dimercaprol injections; *D*, record taken on April 26, 1952, after third series of dimercaprol injections.

Neurological examination revealed only very slight tremor and intention tremor in her left arm; there was no "wing beating." Motor power in her left extremities almost equaled that of the right. There was some increase of tone in her left leg. Deep reflexes were active but equal on the two sides. A Babinski sign was elicited on the left side.

Laboratory findings in the blood and urine were essentially the same as on previous occasions.

A third series of dimercaprol injections was started at the end of January, 1952. At the end of April, 1952, the patient was readmitted for clinical evaluation and for the fourth course of dimercaprol treatments. The improvement in her condition had been maintained. The patient was even able to perform finer work, such as sewing and writing. Threading a needle, however, was still somewhat difficult.

At the time of writing, the patient has been under our observation for more than seven months since the commencement of dimercaprol therapy. There have been no signs of regression in her clinical condition.

Electroencephalographic Observations.—Concomitant with the clinical observations, electroencephalographic studies were done on the patient. Altogether, 10 records were taken during therapy and in the treatment intervals. While the three pretreatment records displayed a considerable degree of abnormal activity, we were struck by the observation that the subsequent records showed marked diminution of this abnormality. In Figure, *B*, *C*, and *D* this gradual and progressive improvement is demonstrated. There occurred a lessening in the incidence of pathological slow activity and of the bursts. The last record (Fig., *D*), obtained six months after the onset of treatment, shows an acceleration of the basic rhythm (7½ to 9½ cps) and little slow pathological activity with no potentials slower than 4 cps. Several short bursts were seen only during and after hyperventilation.

COMMENT

The patient described in this study had had hepatolenticular degeneration for four years prior to the onset of dimercaprol therapy. Like the other eight successfully treated patients whose cases have been reported in the literature, this patient had the "pseudosclerotic" form. At the time that the treatment was begun she displayed a severe degree of disability. Improvement began to manifest itself during the second week of treatment, progressed for the following three months, and has been maintained since. At the time of writing, more than seven months since the commencement of treatment, the duration and high degree of improvement can hardly be conceived of as representing a natural remission of the disease.

The pathophysiology of hepatolenticular degeneration is not yet completely understood. Pathological and clinical investigations seem to indicate that there exists a defect in copper metabolism, in the direction of an excessive absorption of this metal.[4] The aim of dimercaprol administration is mobilization and excretion of the excessive copper of the tissues. Restriction of copper intake does not seem practicable, a point recently stressed by Denny-Brown and Porter,[4] but it might be of interest to consider the possibility of using ion-exchange resins, with the intention of diminishing copper absorption from the gastrointestinal tract.

In view of the fact that dimercaprol has been observed to be toxic to animals with hepatic damage,[6] endeavors in this direction might be of considerable practical

6. Cameron, G. R.; Burgess, F., and Trenwith, V. S.: Possibility of Toxic Effects from 2,3-Dimercaptopropanol in Conditions of Impaired Renal or Hepatic Function, Brit. J. Pharmacol. **2**:59, 1947.

interest. Although no important untoward effects have been reported up to this time in patients with hepatolenticular degeneration who have been treated with dimercaprol, it should be kept in mind that these patients will probably require repeated courses of the drug for many years. In fact, the need for caution in administering dimercaprol to patients with impaired liver function has been stressed by Thompson.[7]

The electroencephalogram usually does not reveal abnormalities in patients with hepatolenticular degeneration.[8] It has been stated by Denny-Brown[9] that in the early stages of the disease the electroencephalogram does not reveal any abnormality, and that "only when the patient is considerably disabled by motor disturbances are changes regularly found." In the series reported by Herz and Drew,[10] electroencephalograms were obtained on five patients. All the records were normal. In the cases of Denny-Brown and Porter [4] the tracings of the two patients so examined did not reveal any abnormality. Strauss and colleagues [11] found normal records for the four patients they examined.

The record of the patient examined by Weatherly [12] showed normal potentials most of the time, but now and then outbursts and runs of high-voltage slow activity appeared. A similar disturbance was recorded in the case of Bridgman and Smyth.[13]

The electroencephalographic record of the patient reported in this study showed a marked degree of generalized disturbance with symmetrical outbursts. The diminution in electroencephalographic abnormality recorded concomitantly with the clinical improvement seems to us of considerable interest.

It may be assumed that the elimination of the excessive copper from the brain tissue may explain both the clinical and the electroencephalographic improvement in this patient.

SUMMARY

A case of advanced hepatolenticular degeneration of the pseudosclerotic type, with a marked electroencephalographic abnormality is reported.

The administration of dimercaprol (BAL) resulted in striking clinical improvement, which was paralleled by a remarkable diminution in electroencephalographic abnormality.

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7. Thompson, R. S. H.: Therapeutic Application of British Anti-Lewisite, Brit. M. Bull. **5**:1199, 1948.

8. Schwab, R. S.: Electroencephalography in Clinical Practice, Philadelphia, W. B. Saunders Company, 1951, p. 131.

9. Denny-Brown, D.: Diseases of the Basal Ganglia and Subthalamic Nuclei, New York, Oxford University Press, 1946, p. 302.

10. Herz, E., and Drew, A. C.: Hepatolenticular Degeneration, Arch. Neurol. & Psychiat. **63**:843, 1950.

11. Strauss, H.; Ostow, M., and Greenstein, L.: Diagnostic Electroencephalography, New York, Grune & Stratton, Inc., 1952, p. 88.

12. Weatherly, H.: Progressive Lenticular Degeneration with Electroencephalogram and Pneumoencephalogram, Am. J. Roentgenol. **45**:714, 1941.

13. Bridgman, O., and Smyth, F. S.: Progressive Lenticular Degeneration, J. Nerv. & Ment. Dis. **99**:534, 1944.

ADDENDUM.—By December, 1952, the patient had been observed for a further period of six months. Two additional courses of dimercaprol injections were administered according to the previous scheme, making a total of five courses of dimercaprol treatments.

No further changes were noted in the patient's condition, which remained satisfactory. The amino acid excretion in the urine was found to be 305 mg. in 24 hours on one occasion. It may be relevant to add that for the last five or six months the Babinski sign could not be elicited, although it had been consistently positive before commencement of the treatment. Electroencephalographic examinations showed symmetrical bursts of 3½ to 6 cps. waves during and after overbreathing only, but the records were otherwise within normal range.

TREATMENT OF MULTIPLE SCLEROSIS WITH LOW-FAT DIET

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IN TWO previous papers the hypothesis has been developed that the geographic variations in the incidence of multiple sclerosis are influenced by the average amount of the fat consumed: A high-fat consumption is associated with a high incidence of multiple sclerosis; a low-fat consumption is associated with a low incidence of multiple sclerosis.[1] Evidence has also been presented which suggests that the consumption of relatively saturated milk and animal fats is more likely to be associated with a high incidence of multiple sclerosis than is the consumption of unsaturated vegetable and fish oils. In either event fat intake seems to increase the incidence of multiple sclerosis by precipitating the disease in susceptible persons.

With the information at hand it is not possible to prove that the apparent relationship of high-fat consumption to a high incidence of multiple sclerosis is not due to factors other than fat which have the same geographic distribution as a high-fat intake. The Norwegian nutritional survey[1b] attempted to solve this possible discrepancy, but because the extent of the survey was small in comparison with the total population and because other factors could not be ruled out, a positive correlation cannot be considered to have established a cause-and-effect relationship. In the present paper the effect of low-fat diets on the clinical course of the disease in patients with well-established multiple sclerosis is reported.

MATERIALS AND METHODS

One hundred and fifty patients with multiple sclerosis are being followed on a low-fat diet. As of July, 1952, 47 have been on the diet for 2 to 3½ years or more. These patients all have well-established multiple sclerosis. Many have been admitted one or more times to the Montreal Neurological Institute for study. For the remaining patients the diagnosis has been confirmed independently by neurologists elsewhere.

Classification of Material.—Forty-five of the 47 patients had exhibited periodic exacerbations and remissions since onset of the disease. Early in the disease the remissions were often remarkably complete, and between attacks either the progress of the illness was stationary or the performance of the patient was improved. The length of this early period of disease was presumably variable. Thirty-four of these patients were in this early phase of the disease when first placed on the low-fat diet (Chart 1, Exacerbating-remitting type—early).

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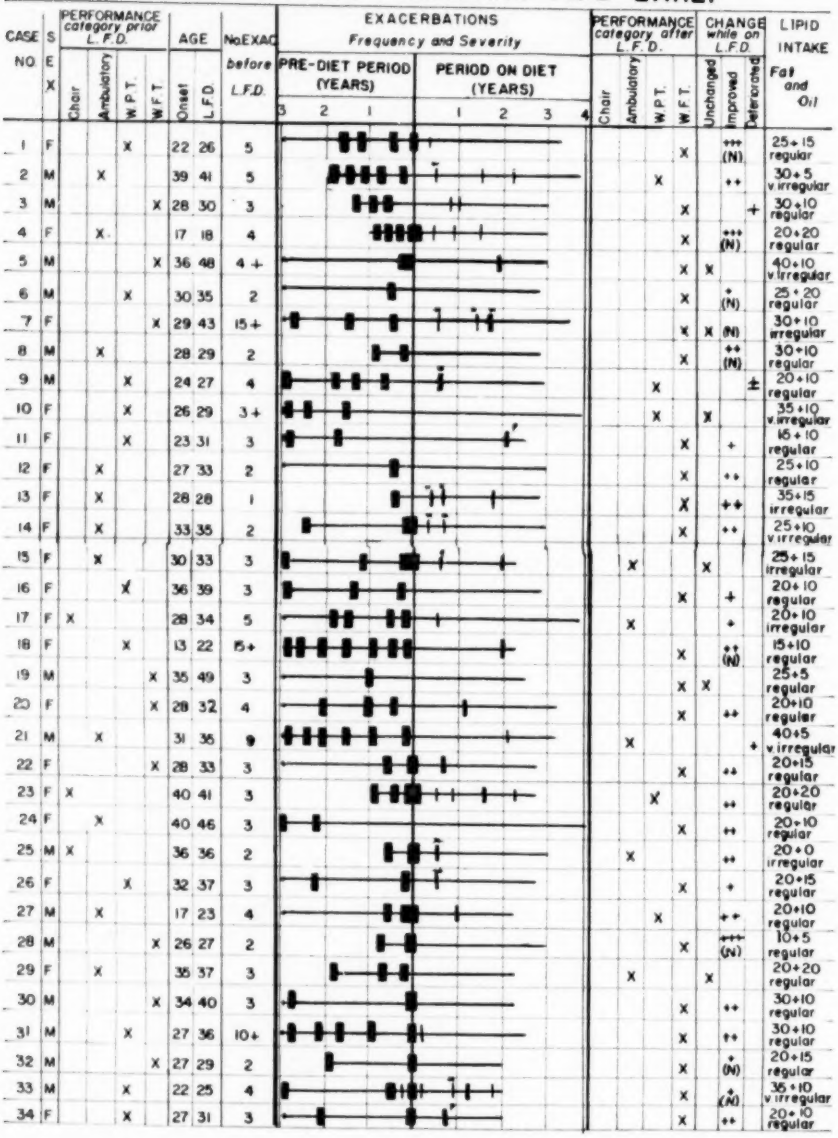
1. (*a*) Swank, R. L.: Multiple Sclerosis: A Correlation of Its Incidence with Dietary Fat, Am. J. M. Sc. **220**:421-430, 1950. (*b*) Swank, R. L.; Lerstad, O.; Strom, A., and Backer, J.: Multiple Sclerosis in Rural Norway: Its Geographic and Occupational Incidence in Relation to Nutrition, New England J. Med. **246**:721-728, 1952.



CASE NO.	S	E	X	Chair	Ambulatory	W.P.T.	W.F.T.	Onset	L.F.D.	No. EXAC. before L.F.D.	PERFORMANCE category after L.F.D. Chair	Ambulatory	W.P.T.	W.F.T.	CHANGE while on L.F.D. Unchanged	Improved	Deteriorated	LIPID INTAKE Fat and Oil
1	F					X		22	26	5				X		+++ (N)		25+15 regular
2	M				X			39	41	5			X			++		30+5 v. irregular
3	M						X	28	30	3				X			+	30+10 regular
4	F				X			17	18	4				X		+++ (N)		20+20 regular
5	M						X	36	48	4+				X	X			40+10 v. irregular
6	M					X		30	35	2				X		+ (N)		25+20 regular
7	F						X	29	43	15+				X	X	(N)		30+10 irregular
8	M				X			28	29	2				X		++ (N)		30+10 regular
9	M					X		24	27	4			X				±	20+10 regular
10	F					X		26	29	3+			X		X			35+10 v. irregular
11	F					X		23	31	3				X		+		15+10 regular
12	F				X			27	33	2				X		++		25+10 regular
13	F				X			28	28	1				X		++		35+15 irregular
14	F				X			33	35	2				X		++		25+10 v. irregular
15	F				X			30	33	3		X			X			25+15 irregular
16	F					X		36	39	3				X		+		20+10 regular
17	F		X					28	34	5		X				+		20+10 irregular
18	F					X		13	22	15+				X		++ (N)		15+10 regular
19	M						X	35	49	3				X	X			25+5 regular
20	F						X	28	32	4				X		++		20+10 regular
21	M				X			31	35	9		X					+	40+5 v. irregular
22	F						X	28	33	3				X		++		20+15 regular
23	F		X					40	41	3			X			++		20+20 regular
24	F				X			40	46	3				X		++		20+10 regular
25	M		X					36	36	2		X				++		20+0 irregular
26	F					X		32	37	3				X		+		20+15 regular
27	M				X			17	23	4			X			++		20+10 regular
28	M						X	26	27	2				X		+++ (N)		10+5 regular
29	F				X			35	37	3		X			X			20+20 regular
30	M						X	34	40	3				X		++		30+10 regular
31	M					X		27	36	10+				X		++		30+10 regular
32	M						X	27	29	2				X		+ (N)		20+15 regular
33	M					X		22	25	4				X		+ (N)		35+10 v. irregular
34	F					X		27	31	3				X		++		20+10 regular

Chart 1.—Data concerning the condition of the patients in the early phase of the exacerbating-remitting type of multiple sclerosis, during the predietary and dietary periods.

In this chart, and in Chart 2, the difference between the age at onset and the age when the low-fat diet (*L. F. D.*) was started gives the total duration of the predietary period of the disease. The patients are divided into four sections according to performance category: chair or wheel-chair patients; ambulant patients; patients working part time (*W. P. T.*), and patients working full time (*W. F. T.*). The degree of improvement or of deterioration is indicated arbitrarily by + to ++++. (*N*) in the "Improved" column indicates that the patient was normal neurologically on July 1, 1952. The average fat intake (lipid intake) is recorded as fat and oil, and the terms "regular" and "irregular" indicate how well the diet was followed. The solid horizontal line indicates the length of the study period prior to and during use of the low-fat diet, and the squares and rectangles on these lines indicate the relative duration and severity of exacerbations and the approximate times of their occurrence. The asterisks above these solid marks indicate that the diet was not being followed at that time, and *p* indicates that the exacerbation occurred at the end of a normal pregnancy.

The early phase of the disease passes insidiously into what I shall refer to as the late, or progressive, phase (Chart 2, A. Exacerbating-Remitting Type—Late Progressive). This phase of the disease is characterized by gradually increasing disability or deterioration whether or not there were exacerbations of the disease. Patients are included in this category only when steady progression of the disease has been clearly established. Eleven patients were so classified at the time they were placed on the low-fat diet.

Only two of the patients had steadily progressive disease from onset and did not exhibit clear-cut "attacks" (exacerbations and remissions) at some time (Chart 2; B. Progressive Type—No Exacerbations).

Forty-one of the patients were ambulant and working part or full time when they were placed on the diet, and the same number were ambulant after the period of therapy reviewed in this paper. In a sense, my colleagues and I selected the patients in an attempt to have as

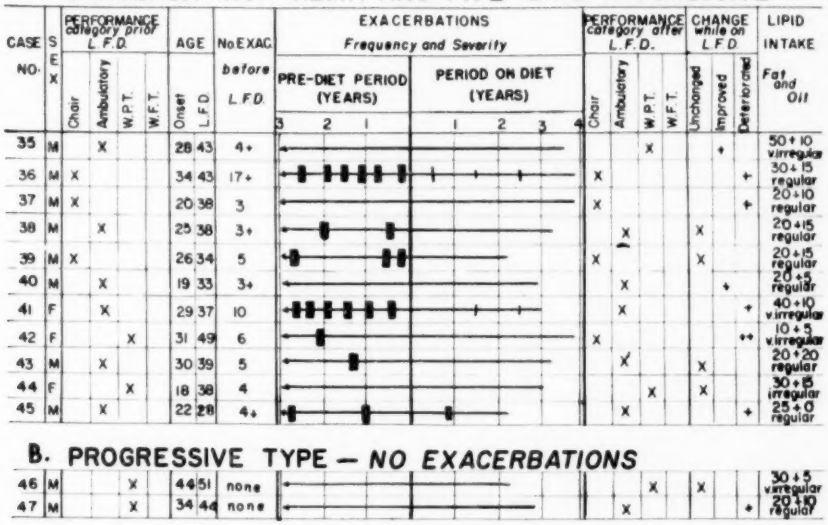


Chart 2.—Data on condition of patients in (*A*) the late progressive phase of exacerbating-remitting multiple sclerosis, and (*B*) the progressive type of the disease with no exacerbations.

many active, working patients as possible under our care. This was done for two reasons: First, it is far easier to evaluate an exacerbation or a remission in an ambulant patient, and, second, the disease seems to be more rapidly progressive in ambulant working patients than in those confined to the wheel chair or to bed.

Control of Material.—We have not a large enough group of patients with multiple sclerosis who consumed a normal diet to compare with those who received a low-fat diet. We have, therefore, used the three-year period preceding the low-fat diet as a control for each of these patients. These data, with other pertinent facts concerning each patient, and the classification of each patient are included in Charts 1 and 2. The frequency and severity of "attacks" of the disease and the general over-all performance of the patient have been used in evaluating the course of the disease before and after going on the diet. We have not evaluated our cases on the basis of a large number of variables (50), as was recently suggested by Alexander,[2] since this method

2. Alexander, L.: New Concept of Critical Steps in Cause of Chronic Debilitating Neurologic Disease in Evaluation of Therapeutic Response: A Longitudinal Study of Multiple Sclerosis by Quantitative Evaluation of Neurologic Involvement and Disability, A. M. A. Arch. Neurol. & Psychiat. **66**:253-271, 1951.

was not available at the beginning of our study. His procedure is cumbersome and probably reduces the subjective element less than he has suggested.

The patient's memory of his illness, even concerning details only a few years past, is often incomplete. He is likely to remember only the severe "attacks." Fortunately, in many instances hospital records have helped to complete the histories of our cases. During the period of observation on patients receiving the low-fat diet all changes in symptoms and signs were recorded except the slight fluctuations which are frequent in patients with definite, although slight, disability. It is not difficult to conclude that a patient is having an exacerbation of disease if he exhibits entirely new signs and symptoms or significant disability from exacerbation of old symptoms and signs. When existing signs and symptoms are intensified slightly, or when those which have cleared entirely return in mild form, one cannot always be certain that fatigue or nervousness alone is not the cause. This is particularly true when the evidence of increased activity lasts but a few hours or days, or when the patient has been exposed to factors causing significant fatigue and nervousness.

In preparing Charts 1 and 2, it has sometimes been helpful to resort to the patient's own judgment of the relative severity of "attacks" during the predietary and dietary period. This procedure is probably of limited value, owing to the desire of almost all patients to be optimistic about the course of their disease and the desire of many to please their physician.

The Low-Fat Diet.—The low-fat diet contains less than 40 gm. of fat. This is about one-third the average fat intake in the Montreal area for both normal persons and patients with multiple sclerosis not on a diet when the fat intakes are estimated from records similar to those kept by the patient, as outlined in this paper. Since the diet was first adopted, some changes have been made in the type of fat to be allowed. For the first year the diet contained 20 to 30 gm. of fat, mostly milk and animal fat.[3] In the subsequent two years the (saturated) animal and milk fats were limited to 20 gm. daily, and to this was added 5 gm. of cod liver oil and 10 to 15 gm. daily of vegetable oil or fish oil. In the past year the milk fat has been eliminated from the diet so far as possible and replaced by animal fat and other hard fats, such as margarine and shortening. Because the increased animal fat has been ingested largely in meat, an increase has resulted in the animal-protein intake. The protein intake is maintained at 50 gm. or more daily, depending on the weight of the patient, and the balance of the caloric need is obtained from carbohydrates. The caloric intake has been low, averaging about 1,700 calories for a 130-lb. (59-kg.) woman and 1,900 calories for a 145-lb. (65.8-kg.) man. These figures may be low, however, since our patients were primarily concerned with recording their fat intake and may have forgotten to record other foods at times. One multiple-vitamin capsule, containing vitamins A, D, C, and B complex, is taken daily, and whole-wheat bread is recommended. Skim milk is used by all patients as a source of protein, and most patients eat at least one egg daily.

The dietary intake of the patients is checked every two weeks at first and later at monthly intervals. The patient records all the food he eats for each meal in a notebook provided for this purpose. From this the dietitian determines the food intake and makes necessary adjustments. The patient's weight is checked at each visit, and rapid changes in weight are carefully watched for. The diet is mimeographed, and substitutions are provided to prevent the diet from becoming uninteresting ("Appendix"). Special recipes substituting vegetable oils for animal and butter fats have been assembled and are furnished to the patient.

Various supportive measures, such as physical therapy, use of drugs to relieve nervous tension, and other medical treatments, have been employed as indicated. In this group of patients none of the ambulant and only a few of the nonambulant patients have received physical therapy regularly.

3. The average iodine numbers of the fats mentioned in this section are as follows:

Milk fat	46 to 55	Vegetable oil	90-110
Animal fat	60 to 65	Fish oil	90-180
Margarine	approximately 70	Cod liver oil	150-180

The iodine values indicate the degree of unsaturation of the fatty acids contained in the lipids. The milk and animal fats and margarine are relatively saturated fats and are solid at room temperatures; the oils are relatively unsaturated and are fluid at these same temperatures.

RESULTS

Effect of Low-Fat Diet on General Performance of the Patient.—Early Exacerbating-Remitting Type (Chart 1): Of the 34 patients in this group, all but 3 were ambulant when placed on the low-fat diet. The three chair patients were either ambulant (Cases 17 and 25) or working part time (Case 23) after the period of treatment under review. Three of the remaining patients (Cases 3, 9, and 21) showed slight or questionable deterioration, although this was not pronounced enough to lower the performance-category classification for any one of them. The performance category and general condition of six other patients (Cases 5, 7, 10, 15, 19, and 29) were unchanged. The remaining 22 patients showed slight (+) to pronounced (+++) improvement generally, and for 17 the performance category rose. Thus, of the 34 patients in this group, 3 showed evidences of slight deterioration, the status of 6 was unchanged, and the remaining 25 showed slight to pronounced improvement during consumption of the low-fat diet for a period averaging 2.8 years a patient. The treatment periods varied from 2 to 4.2 years.

Late Progressive Exacerbating-Remitting Type (Chart 2): Of the 11 patients in this group, 3 were confined to a chair. Six of the remaining patients were ambulant, and two were working part time prior to going on the diet. Five of these patients exhibited slight to moderate deterioration; the status of four remained unchanged, and two showed slight improvement during the period of the test on the diet. The performance category fell for one patient, remained the same for nine, and improved for one. The average period of observation for this group of patients was approximately 3 years, with a range of 2.2 to 3.7 years.

Progressive Type—No Exacerbations (Chart 2): Of two patients in this group, the status of one remained unchanged and that of the other deteriorated.

Effect of Low-Fat Diet on Severity and Frequency of Exacerbations of the Disease.—Early Exacerbating-Remitting Type (Chart 1): During the period prior to going on the low-fat diet, 34 patients, in an aggregate period of 83.4 years (average, 2.4 years per patient), had 96 exacerbations of the disease, an average per patient of one exacerbation every 10 to 11 months.[3a] During consumption of the low-fat diet for an aggregate period of 95.1 years, the same patients had 40 exacerbations, of which 13 occurred after dietary indiscretions, during which the fat intake was increased 100% or more for several days to several weeks. Two other patients had exacerbations following termination of normal full-term pregnancies. The average length of time between exacerbations during the period on the low-fat diet was nearly 30 months when all attacks are considered, or 42 months when the attacks following dietary indiscretions are eliminated.

It is important to note that 24 of the 40 exacerbations, if all are considered, or 13 of the 27 exacerbations, if those occurring after dietary indiscretions are eliminated, occurred during the first year on the diet. Thus, the incidence per year of exacerbations during the first year on the diet was approximately twice that during the subsequent 1.8 years on the diet. This does not include the two exacerbations

3a. In a preliminary report, Paul Thygeson (Analysis of the Course of Multiple Sclerosis, Acta psychiat. et neurol., Supp. 74, pp. 48-49, 1951) noted that on the average an outburst of activity (exacerbation) occurred every 10 months.

occurring immediately after termination of normal pregnancies. Fifteen of the patients were placed on the low-fat diet during or near the end of an exacerbation, and 19, during remission of the disease.

During the period on the diet the exacerbations were significantly less severe and much shorter than those the patients had experienced prior to this regimen. In many cases incidents recorded as exacerbations, and shown in Chart 1, either were not regarded by the patient as exacerbations or were considered extremely mild. In only 12 instances were the attacks similar in severity to those experienced before the patients went on diet, and then they were identified as mild. It is of further interest that the attacks almost always consisted of an intensification of preexisting symptoms. In eight patients (Cases 1, 3, 4, 5, 9, 22, 31, and 33) symptoms and signs not previously noted developed during exacerbation, but these were mild.

Late Progressive Exacerbating-Remitting Type (Chart 2): During the period prior to institution of the low-fat diet 11 patients, in an aggregate period of 33 years, had 21 exacerbations of disease (an average of one attack every 18 months). While on diet the same patients, in an aggregate period of approximately the same time, had six exacerbations, an average of one attack every 66 months. These exacerbations were almost all much milder than the patients had experienced prior to going on the diet and consisted of an intensification or reappearance of preexisting symptoms and signs.

Progressive Type-No Exacerbations (Chart 2): No exacerbations were noted.

Importance of Strict Dietary Control.—Rigid dietary control, particularly during the first year, seems to be important if maximum benefit from the low-fat diet is to be obtained. This is indicated by the greater incidence of exacerbations during the first year on the diet, during which the patients were learning how to follow the diet. The occurrence of exacerbations in 13 instances after significant increases in the fat intake is additional evidence in support of this contention. It has been our impression that those persons who followed the diet intelligently have in general done much better than those either incapable of following, or unwilling to follow, the diet carefully.

It has also been observed that patients who are underweight by all accepted weight-height standards do better than those who are overweight. The majority of our patients were underweight when the low-fat diet was initiated, and many lost 5 to 10 lb. (2.3 to 4.5 kg.) during the first two months on the diet. Weight usually became stabilized at that point and remained stationary. Exacerbations of disease have followed unexplained rapid loss or gain in weight often enough to be watched for carefully. The relation of loss or gain in weight to exacerbation has been described by Brickner and Brill.[4] It is our belief that the loss in weight before exacerbation is not the cause of the exacerbation, but a part of it. Gain in weight, however, may be a factor in causing exacerbation.

It should be pointed out that some patients have a tendency to consume far less fat than prescribed, particularly when they first go on the diet. This may cause them to feel weak and listless. On several occasions, patients who were under strict dietary control for about a year were requested to consume as little fat as

4. Brickner, R. M., and Brill, N. Q.: Dietetic and Related Studies on Multiple Sclerosis, Arch. Neurol. & Psychiat. **46**:16-35, 1941.

possible. In a period of about three weeks they became generally weak. An increase of the fat intake to the former level of 20 to 30 gm. daily in these cases was soon followed by a return of strength. The development of generalized weakness when the fat intake was very low is probably not related to an essential fatty-acid deficiency, such as that described by Burr, Burr, and Miller,[5] but a satisfactory explanation of this symptom cannot be given.

EVALUATION OF RESULTS

Our results suggest that the low-fat diet used in this study was beneficial to a large percentage of our 47 patients with multiple sclerosis. It seemed to be beneficial particularly to those in whom the disease was in its early phase. The period of trial was long enough to be of some significance, since it included two or more exacerbation-remission cycles in most cases, and since the patients seemed to do better during the second and third than during the first year of therapy. Moreover, less than half the patients were placed on the diet immediately after exacerbation, so that extended periods of remission could not have been anticipated in the majority. The disease was not cured, since clear-cut exacerbations were noted in patients on diet. However, the reduction in severity and frequency of the exacerbations was substantial. This was indicated by the many patients who improved generally and were capable of increased work after a period of three years, despite the occurrence of mild exacerbations during this time. The steady progression of well-developed signs and symptoms was not stopped by the low-fat diet, even though exacerbations when they occurred were less severe and frequent. If the course of the disease is to be significantly altered, it seems necessary to start treatment early.

Adequate control for our results is not available. Nathanson [6] has pointed out how variable the disease can be in two control groups of the same size. Müller's [7] extensive study of the natural course of multiple sclerosis in Sweden has shown that the activity of the disease, as measured by the number of exacerbations, varies with its duration; during the first five years the average number, or frequency, of exacerbations exceeds the number to be expected later in the disease. These observations indicate a necessity for caution in judging the effects of any therapy on the course of multiple sclerosis. We have attempted to compare our results with those obtained by Putnam, Chiavacci, Hoff, and Weitzen [8] but find this unsatisfactory, since their patients were not followed as long as ours and since many of their patients were in the chronic progressive phase of the disease when first observed. In a study of cases of multiple sclerosis in and around Rochester, Minn., MacLean, Berkson, Woltman, and Schionneman [9] observed that approx-

5. Burr, G. O.; Burr, M. M., and Miller, E. S.: On Fatty Acids Essential in Nutrition, J. Biol. Chem. **97**:1-9, 1932.

6. Nathanson, M.: Problems in Evaluating Treatment in Multiple Sclerosis, Am. J. Med. **12**:593-595, 1952.

7. Müller, R.: Studies on Disseminated Sclerosis with Special Reference to Symptomatology, Course, and Prognosis, Acta med. scandinav. Supp. *222*, 1949.

8. Putnam, T. J.; Chiavacci, L. V.; Hoff, H., and Weitzen, H. G.: Results of Treatment of Multiple Sclerosis with Dicoumarin, Arch. Neurol. & Psychiat. **57**:1-13, 1947.

9. MacLean, A. R.; Berkson, J.; Woltman, H. W., and Schionneman, L.: Multiple Sclerosis in a Rural Community, A. Res. Nerv. & Ment. Dis., Proc. (1948) **28**:25-27, 1950.

imately 4% of their patients each year became disabled in terms of walking or working. Among our patients a general over-all improvement in the performance category at the rate of more than 10% per year was noted. The Rochester series of patients is not strictly comparable to the series reported in this paper, since we have been concerned primarily with early cases, and since the geographic site of their study was far removed from ours. Even in our group with more advanced disease (Chart 2; exacerbating-remitting type—late progressive; and progressive type—no exacerbations) only two patients showed significant deterioration and one patient's condition improved. The average deterioration rate for this group of 13 patients, therefore, was approximately 3%. We are aware of the difficulties of controlling a study such as we have undertaken, and find that we have been left with a choice of controlling our study by comparing the pretreatment and the treatment course of the disease, or of following simultaneously two large patient groups, comparable with regard to time and geographic location. The latter was not possible.

COMMENT

Evidence is accumulating to suggest that a diet low in fat is beneficial to patients with multiple sclerosis. It is of interest to consider some of the means by which the fat intake might influence the course of this disease.

First, there is reason to suspect a vascular component in the pathogenesis of the disease. Some of the clinical features which suggest this have been outlined by Putnam [10] and Brickner.[11] The observations of tortuous and irregular blood vessels in the nail beds,[12] and of these and other peripheral vascular phenomena described and discussed by Grain and Jahsman,[13] indicate that the vascular system sustains damage in this disease. The fact that many other conditions exhibit similar vascular phenomena is indicative of the complexity of the situation rather than of the lack of significance of the changes. The observation of Franklin and Brickner [14] that spasms of the retinal arteries were present during transient episodes of scotoma in patients with multiple sclerosis, and that of Rucker [15] of sheathing of the retinal veins emphasize the importance of the vascular system in this disease. The increase in capillary fragility reported by Shulman, Alexander, Ehrentheil, and Gross [16] may be further indication that the vascular system is defective in multiple sclerosis.

10. Putnam, T. J.: Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:786-790, 1933.

11. Brickner, R. M.: Significance of Localized Vasoconstrictions in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. (1948) **28**:230-244, 1950.

12. (*a*) Gomirato, G.: Alterazioni dei capillari in malati di sclerosi multipla e loco significato, Riv. pat. nerv. **53**:148-156, 1939. (*b*) Chiavacci, L. V., and Putnam, T. J.: Capillaroscopic Observations in Cases of Multiple Sclerosis, Arch. Neurol. & Psychiat. **61**:577-582, 1949.

13. Grain, G. O., and Jahsman, W. E.: Significance of Peripheral Vascular Changes in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. (1948) **28**:216-235, 1950.

14. Franklin, C. R., and Brickner, R. M.: Vasospasm Associated with Multiple Sclerosis, Arch. Neurol. & Psychiat. **58**:125-162, 1947.

15. Rucker, C. W.: Sheathing of the Retinal Veins in Multiple Sclerosis, J. A. M. A. **127**:970-973, 1945.

16. Shulman, M. H.; Alexander, L.; Ehrentheil, O. F., and Gross, R.: Capillary Resistance Studies in Multiple Sclerosis, J. Neuropath. & Exper. Neurol. **9**:420-429, 1950.

Second, the observation of clumped or aggregated red blood cells in the circulation, referred to as "sludging" of the blood by Kniseley and colleagues [17] and by Roizin, Abel, and Winn [18] may contribute to the development of our hypothesis. The presence of "sludging" in other conditions, which was noted by both groups of investigators, suggests that other critical circumstances are necessary before multiple sclerosis develops, that there is something peculiar about "sludging" which occurs in multiple sclerosis, or that "sludging" is of no pathologic significance. Intravascular aggregation of the red blood cells was first noted by Lister [19] in the injured wing of the bat, but the observation by Kniseley and associates [20] of this phenomenon in monkeys in the terminal stages of malaria attracted a great deal of attention. Kniseley and associates observed that the aggregations of erythrocytes were held together by glassy precipitates, which were identified by microprobing in vitro. The aggregates of erythrocytes ("rafts") were seen in vivo lodged at the capillary junctions blocking the blood flow. Lutz, Fulton, and Akers [21] pointed out that the presence of sludged blood in man has been determined under conditions which do not permit clear visualization and adequate testing for the presence of a sticky coat binding erythrocytes together. These workers noted that in the hamster the erythrocytes frequently have a tendency to circulate in groups owing to vasomotor rhythmicity and consequent plasma skimming (a phenomenon which was described by Fowler [22] after stimulation of vasoconstrictor nerves and intravascular injections of vasoconstrictor substances and reported as "sludged blood"). They further suggested that Kniseley had "extended his concept, without crucial evidence, to include blood flow characteristics which differ from those of the sludged blood he originally defined." Lutz and associates also stated that other investigators had confused the classic rouleau formation of Fahraeus with the concept of sludged blood, and that the "term 'sludged' blood is obviously a misnomer in the majority of circumstances in which it has been used."

It is evident that the presence of aggregated or clumped red blood cells in the blood vessels of the nail bed or cornea of man can, by itself, be misleading. If in addition an abnormal adhesiveness of the blood elements can be demonstrated, greater significance might be attributed to this phenomenon. Swank [23] observed

17. Kniseley, M. H.; Block, E. H.; Eliot, T. S., and Warner, L.: Sludged Blood, Science **106**:431-440, 1947.

18. Roizin, L.; Abel, R., and Winn, J.: Preliminary Studies of Sludged Blood in Multiple Sclerosis, Proceedings of the American Academy of Neurology, 1952.

19. Lister, J.: On Early Stages of Inflammation, Proc. Roy. Soc. London, s.B **17**:429, 1857; cited by Thorsen, G., and Hint, H.: Acta chir. scandinav., Supp. 154, 1950.

20. Kniseley, M. H.; Stratman-Thomas, W. K.; Eliot, T. S., and Bloch, E. H.: Knowlesi Malaria in Monkeys: I. Microscopic Pathological Circulatory Physiology of Rhesus Monkeys During Acute Plasmodium Knowlesi Malaria (A Motion Picture), J. Nat. Malaria Soc. **4**:285-300, 1945.

21. Lutz, B. R.; Fulton, G. P., and Akers, R. P.: White Thromboembolism in the Hamster Cheek Pouch After Trauma, Infection and Neoplasia, Circulation **3**:339-351, 1951.

22. Fowler, E. P.: Capillary Circulation with Changes in Sympathetic Activity: I. Blood Sludge from Sympathetic Stimulation, Proc. Soc. Exper. Biol. & Med. **72**:592-594, 1949.

23. Swank, R. L.: Changes in Blood Produced by a Fat Meal and by Intravenous Heparin, Am. J. Physiol. **164**:798-811, 1951.

clumping and adhesiveness of the red blood cells in vitro in whole blood obtained from dogs and human beings who had received large fat meals some hours before (Fig. 6, Swank [23]). Changes in the sedimentation rates, hematocrit readings, and thrombocyte counts were also noted. These changes in the suspension stability of the blood elements were shown by Swank, Franklin, and Quastel [24] to be accompanied by changes in the plasma-protein pattern in paper chromatography. Similar clumping and adhesiveness of washed red blood cells suspended in solutions containing substances with large molecular weights, such as dextran, were also noted by Thorsen and Hint [25] (their Figs. 14 and 15). These authors stated that the strength and structure of the red blood cell masses which form under these circumstances depend upon the mechanical properties of a surface film which develops upon the red blood cells. This surface film forms from the suspension fluid when the concentration of the colloids or the molecular weights of the colloids in the suspension fluid reach a critical level. The film forms between the suspended red blood cells and the suspension fluid and disappears when the red blood cells are resuspended in saline. One can only wonder whether the complex lipoproteins of very large molecular size which are formed in the blood after large fat meals can be the cause of the aggregation and adhesiveness of the blood elements observed by Swank,[23] and whether the changes in the proteins described by Swank, Franklin, and Quastel [24] are an indication or a result of these changes. Whether the phenomenon of adhesive clumping ("sludging") will prove to be of etiological significance in multiple sclerosis is at present conjectural. A further exploration of this possibility would seem of value.

To determine whether patches of partial ischemia from a critically slowed circulation, such as could result from tightly adherent aggregations of blood elements, might produce demyelinating lesions in the central nervous system, Swank and Hain [26] injected large numbers of paraffin emboli containing lampblack into the carotid artery or the left ventricle of the heart of dogs. It was found that large emboli occluded the larger arteries and produced multiple infarcts with softening, without predilection for any one part of the brain. Small emboli, varying from less than 4 to 15 and 17 μ in diameter lodged temporarily in or passed slowly through the precapillaries and capillaries and produced lesions predominantly in the central white matter and the junction between the white and the gray matter. Many of these lesions consisted of areas of demyelination crossed by normal-appearing axis-cylinders. Other lesions were more destructive, and some had central areas of softening. In all lesions a slight to moderate polymorphonuclear leucocyte response occurred initially and lasted about seven days. In the older demyelinated lesions there was a piloid astrocytosis.

24. Swank, R. L., Franklin, A. E., and Quastel, J. H.: Effects of Fat Meals and Heparin on Blood Plasma Composition as Shown by Paper Chromatography, Proc. Soc. Exper. Biol. & Med. **75**:850-854, 1950.

25. Thorsen, G., and Hint, H.: Aggregation, Sedimentation and Intravascular Sludging of Erythrocytes: Interrelation Between Suspension Stability and Colloids in Suspension Fluid, Acta chir. scandinav., Supp. 154, 1950.

26. Swank, R. L., and Hain, R. F.: Effect of Different-Sized Emboli on the Vascular System and Parenchyma of the Brain, J. Neuropath. & Exper. Neurol. **11**:280-299, 1952.

The demyelinating lesions produced by injections of the small emboli are not identical with the lesions of multiple sclerosis, but points of similarity in the appearance of the lesions are difficult to disregard. The lesions seem to be the result of a temporary or partial local ischemia as a result of marked slowing of the circulation, such as might be expected from pronounced aggregation and stickiness of the blood elements. Most of the paraffin emboli were delayed for only a few to approximately 30 minutes in the precapillaries and capillaries in their passage through the brain; 24 to 48 hours later only an occasional embolus was to be seen in the brain.

Further investigations by Lewis and Swank,[27] using the brains of the animals employed in the study by Swank and Hain,[26] showed that a perivascular gliosis, due to hypertrophy of astrocytic and oligodendroglial fibers, developed around the smaller arterioles and capillaries after a single injection of emboli. These lesions persisted as long as 120 days. These changes might alter the resistance of the blood vessels to the flow of blood and also interfere with the exchange of nutrients and metabolites between the blood and the tissues. The possibility that in multiple sclerosis the tortuosity of the capillary loops of the nail bed,[12a] sheathing of the retinal veins,[15] and increased capillary fragility [16] are caused by transient episodes of ischemia, in the manner of the periarteriolar and pericapillary gliosis described by Lewis and Swank,[27] is worthy of consideration.

Despite the observations of "sludging," definite and direct evidence of significant altered suspension stability of the blood in patients with multiple sclerosis is not available at present. The observation by Swank, Franklin, and Quastel [28] that the plasma-protein pattern in paper chromatography was frequently abnormal in patients with multiple sclerosis raises the question whether a plasma-protein abnormality and a suspension instability of the blood are not etiologically important in this disease. The recent demonstration with the ultracentrifuge (Aird, Gofman, Jones, Campbell, and Garoutte [29]) of a circulating abnormal lipoprotein during activity of multiple sclerosis would appear to confirm the observation of Swank, Franklin, and Quastel [28] on plasma proteins in this disease. At the same time it could link the disease to lipid metabolism.

Fog [30] has recently noted conspicuous decreases in the number of circulating thrombocytes in patients with multiple sclerosis during activity of the disease. The thrombocytes also decrease in normal dogs and man after large fat meals (Swank [23]) and have been seen to decrease in number in the circulation after injections of heparin,[31] when they have been observed to occlude the smaller blood vessels.[32] It

27. Lewis, R. V., and Swank, R. L.: Effect of Cerebral Microembolism on the Perivascular Neuroglia, J. Neuropath. & Exper. Neurol., to be published.

28. Swank, R. L.; Franklin, A. E., and Quastel, J. H.: Paper Chromatography of Blood Plasmas in Multiple Sclerosis, Proc. Soc. Exper. Biol. & Med. **76**:183-189, 1951.

29. Aird, R. B.; Gofman, J.; Jones, H. B.; Campbell, B., and Garoutte, B.: Ultracentrifuge Studies on Lipoproteins in the Cerebrospinal Fluid and Serum of Patients with Multiple Sclerosis, Proceedings of the American Academy of Neurology, 1952.

30. Fog, T., On the Pathogenesis of Multiple Sclerosis, Acta psychiat. et neurol., Supp. 74, p. 22, 1951.

31. Copley, A. L., and Robb, T. P.: Studies on Platelets: Effect of Heparin in Vivo on the Platelet Count in Mice and Dogs, Am. J. Clin. Path. **12**:563-570, 1942.

32. Copley, A. L.: Embolization of Platelet Agglutination Thrombi in the Hamster's Pouch Produced by Heparin, Federation Proc. **7**:22-23, 1948.

is known that heparin is liberated during anaphylactic shock, and the possible significance of this as an etiological agent in multiple sclerosis by altering the suspension stability of the blood is to be considered. It is to be noted that many of the changes in the circulation produced by large fat meals are also produced by injections of heparin.[33]

It is further to be noted that high-fat meals decrease the clotting time of the blood.[34] This observation is of interest because of the well-known hypothesis of Putnam that the lesions of multiple sclerosis are due to cerebral venous thrombosis.[35]

In the past two years we have noted a seasonal trend in activity of multiple sclerosis. This seasonal activity, spoken of before by Ziegler,[36] usually consists of an intensification of existing signs and symptoms which in many cases is of a degree probably insufficient to be classified as an exacerbation, but which rather, is to be designated as a fluctuation. This activity has occurred at times which corresponded with seasonal changes from fall to winter and, again, winter to spring. In the Montreal area the temperature during these periods has shown remarkable daily variations.

SUMMARY AND CONCLUSIONS

Three and one-half years' experience with a low-fat diet in the treatment of multiple sclerosis is summarized. This diet appears to lessen the severity of the disease by reducing the frequency and severity of the exacerbations. Its usefulness seems greatest early in the disease, before significant disability and a steady progression of symptoms have developed. A final conclusion regarding the value of the low-fat diet will have to await a longer trial of this therapy than at present can be reported.

The mechanism by which the fat intake might influence the disease is discussed. Serious consideration is given to the hypothesis that patients with multiple sclerosis have a basic defect in the suspension stability of their blood, which is upset by the hyperlipemia following heavy-fat meals.

APPENDIX

LOW-FAT, HIGH-CARBOHYDRATE, MODERATE-PROTEIN DIET

A copy of the diet is appended.

Your diet will contain 4 tsp. (20 cc.) of hard fats (animal fats, margarine, lard, and shortening) and 4 tsp. of vegetable oil or a substitute a day. In as far as possible the intake of fat should be evenly distributed throughout the day. All patients should consume one egg and 1 tsp. (5 cc.) of cod liver oil daily. Fats or oils used for cooking or baking are counted in the daily allowance of these foods.

33. Swank.[23] Swank, Franklin, and Quastel.[24]

34. Waldron, J. M.; Beidelman, B., and Duncan, G. G.: Inhibition of the Clot-Accelerating Property of Ingested Fat by Simultaneous Feeding of Sugar, J. Appl. Physiol. **4**:761-763, 1952.

35. Putnam, T. J.: Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929-940, 1936.

36. Ziegler, L. H.: Multiple Sclerosis: A Clinical Review and Follow-Up Study, Minnesota Med. **12**:778-783, 1929.

Foods Forbidden on Your Diet

Whole milk, butter, cream, cocoa, and chocolate, and all foods containing these substances, such as pastries, pies, steamed puddings, cake puddings, cakes, cookies, doughnuts, chocolates, chocolate bars, cocoa, hot chocolate, chocolate-flavored drinks, cheese, ice cream, and cream sauce made with butter and whole milk, and canned spaghetti with meat or meat sauce.

Foods Permitted in Any Quantity

Boiled codfish, halibut or haddock, scallops, lobster, crab—any fish which contains no oil
All vegetables
All clear soups
White or brown bread
All cereal products
Skim milk
Cottage cheese (not creamed)
All fruits
Desserts made from egg whites
Cream soup made with skim milk
Maple and corn syrup
Water ice
Seasonings
Rice, tapioca, or cornstarch puddings made with skim milk, no egg yolk
Jello
Fruit juices
Vegetable juices
Clear tea or coffee
Carbonated beverages
Jam
Jelly
Molasses
Marmalade
Honey
Sugar
Spaghetti or macaroni
Fresh or tinned clams and oysters

Foods Permitted in Limited Quantity

Soda crackers
Graham wafers
"Social teas"
Arrowroot biscuits
Ritz® biscuits

Substitutes for 1 Teaspoonful of Hard Fat

2 oz. (60 gm.) chicken, beef, roast leg of lamb, ham, veal, beef sausage, liver, and turkey
1 egg
3 slices bacon, fried crisp and drained well
1 slice of Bologna, **salami**, or liverwurst
1 frankfurter
1 pork sausage
1 slice of roast pork
1 oz. goose or duck
1 tsp. margarine, lard, or shortening
½ lamb chop
½ pork chop

Substitutes for 1 Teaspoonful of Vegetable Oil

1 tsp. of olive oil, corn oil, cottonseed oil, wheat germ oil, mazola,® cod liver oil
5 olives
2 tsp. of salad dressing
15 peanuts
2 tsp. pure peanut butter (not hydrogenated)
2 oz. tuna fish, trout
2 oz. of canned or fresh salmon
1 oz. of mackerel
1 oz. of herring, sardines, or kippers
4 small anchovies

HISTAMINE THERAPY IN ACUTE ISCHEMIA OF THE BRAIN

A Report of Fifty New Cases

A. R. FURMANSKI, M.D.

With the Clinical Collaboration of W. Eckhardt, M.D.; A. Vida, M.D.; H. Ostrander, M.D.; R. F. Biggy, M.D.; S. Bruson, M.D., and F. O. Westfall, M.D.

ENCINO, CALIF.

IN A RECENT paper, the use of intravenous injections of histamine in 25 cases of acute ischemia of the brain was described.[1] The present paper reports experiences in an additional 50 cases. A team of one neurologist (A. R. F.) and six internists treated the 50 patients in a general hospital as part of a large group practice. The minimum of selectivity was used to determine the limits of histamine therapy. Patients with gross cerebral hemorrhage, cerebral edema, intracranial neoplasm, and terminal cardiac failure were not included in this study.

METHOD OF EVALUATION OF THERAPY

In order to evaluate more critically the results of therapy, my colleagues and I have used a quantitative and qualitative system to designate the neurological dysfunction before and after histamine therapy. Each case is tabulated so that our standards of improvement can be compared with those of other investigators, without the semantic difficulties that so easily arise.

The following quantitative scale was used. Each + signifies a unit of dysfunction.

—: No significant dysfunction demonstrable

+: Function present and serviceable, but when it was compared with its previous level or with the normal, impairment was evident (mental dullness; lack of motor dexterity; relative hypalgesia)

++: Function present but so impaired that it was of little serviceable value (mental confusion or stupor; motor paresis; hypalgesia)

+++: No function present (coma; complete motor paralysis; analgesia)

The significant major divisions of the nervous system were used as the qualitative portion of the evaluation. A functional-anatomical system was utilized. The following 16 divisions were used:

Cerebral: mental alertness; speech in writing, speaking, auditory understanding, and reading; motor, arm and leg; sensory, arm and leg; visual fields

Brain stem: coordination, arm and leg; motor, eyes; motor, bulbar; sensory, bulbar; vestibular

RESULTS OF THERAPY

When the results were evaluated according to the criteria indicated above, the 50 patients could be divided into three groups: Thirty in whom a reduction of 75% or more of the units of dysfunction followed therapy were designated as showing

From the Ross Loos Medical Group, Los Angeles.

1. Furmanski, A. R.: Histamine Therapy in Acute Ischemia of the Brain, Arch. Neurol. & Psychiat. **63**:415 (March) 1950.

TABLE 1.—*Clinical Data in Fifty Cases*

Case No.	Age	Sex	Pertinent Data	Neurological Dysfunction		
				Field Involved	Before	After
			Group I			
1	82	M	Sudden onset with dyspnea and generalized weakness; pneumonitis present; histamine begun on 3d day, given for 11 days	Mental Vestibular	++ +	– –
2	62	F	Transient left hemisensory loss 2 wk. before; hypertension for 4 yr.; histamine begun on 5th day, given for 12 days	Mental Motor, leg	+ +++	– –
3	60	F	Hypertension present; transient right hemiparesis 3 yr. before; histamine begun on 1st day, given for 3 days	Sensory, arm Sensory, leg	++ ++	– –
4	42	M	Histamine begun on 1st day, given for 3 days	Motor, arm Sensory, arm	++ ++	– +
5	48	M	Diabetes, poorly controlled for 19 yr.; hypertension for 4 yr.; transient numbness in right hand 1 yr. before; histamine begun on 1st day, given for 11 days	Mental Motor, arm Sensory, arm	+ +++ +	– + –
6	57	F	Histamine begun on 2d day, given for 7 days	Motor, arm Sensory, arm Sensory, leg	+ ++ ++	– – –
7	71	F	Diabetes for 4 yr.; dizziness and progressive stupor for 4 days; blood sugar 139 mg./100 cc.; blood carbon dioxide 46 vol. %; histamine given on 4th day for 4 days; cardiac insufficiency present	Mental Vestibular	+++ ++	– –
8	72	M	Dizziness 1 wk. before; histamine begun on 6th day, given for 11 days; cardiac insufficiency on effort	Visual field Spatial orientation	+++ ++	+ –
9	78	F	Hypertension for 2 yr.; spinal fluid normal except pressure of 220 mm. of water; histamine begun on 1st day, given for 7 days; mild congestive failure present	Mental Motor, bulbar	+++ ++	– –
10	75	M	Confusion for 2 mo.; left-sided weakness for 2 wk.; hypertension present; spinal fluid normal; histamine begun on 3d day, given for 2 days	Mental Motor, bulbar Motor, arm Sensory, leg	++ ++ + +	– – – –
11	78	F	Hypertension present; spinal fluid normal; histamine begun on 8th day, given for 9 days	Motor, arm Sensory, arm Sensory, leg	++ ++ ++	– – –
12	64	F	Hypertension for 5 yr.; paresthesias for 4 mo.; histamine begun on 2d day, given for 3 days	Motor, arm Sensory, arm Sensory, leg Visual field	+ ++ ++ +	– – – –
13	60	F	Poorly controlled diabetes with hypertension; intermittent confused for 4 yr.; blood sugar 159 mg./100 cc. and blood carbon dioxide 42 vol. %; histamine begun on 4th day, given for 12 days	Mental Motor, arm Motor, leg	++ ++ ++	+ – –
14	70	F	Hypertension for 10 yr.; spinal fluid normal; histamine begun on 3d day, given for 10 days	Motor, arm Motor, leg Sensory, arm Vestibular	+++ ++ + +	+ – – –
15	71	M	Spinal fluid normal; histamine begun on 1st day, given for 7 days; cardiac insufficiency on effort	Motor, arm Motor, leg Sensory, arm Sensory, leg	+++ ++ + +	+ – – –
16	64	F	Spinal fluid normal except a pressure of 260 mm. of water; histamine begun on 3d day, given for 14 days	Motor, arm Motor, leg Sensory, arm Sensory, leg	+++ +++ + +	+ + – –

TABLE 1.—*Clinical Data in Fifty Cases*—Continued

Case No.	Age	Sex	Pertinent Data	Neurological Dysfunction		
				Field Involved	Before	After
17	71	F	Transient left hemiparesis and aphasia 3 yr. before; hypertension for 20 yr.; spinal fluid protein 65 mg./100 cc.; histamine begun on 8th day, given for 4 days	Speech, motor	+	+
				Speech, auditory	+	+
				Motor, arm (R)	+	−
				Motor, leg (R)	+	−
				Sensory, arm (R)	++	−
				Sensory, leg (R)	++	−
18	70	M	Coronary insufficiency for 3 yr.; cerebral embolism 2 wk. after 4th coronary occlusion; histamine begun on 1st day, given for 9 days; death of 5th coronary attack on 10th day; brain found normal on autopsy	Motor, arm	++	−
				Motor, leg	++	−
				Sensory, arm	++	−
				Sensory, leg	++	−
19	53	F	Diabetes and hypertension for 15 yr.; coronary occlusion 14 mo. before; histamine begun on 3d day, given for 6 days	Motor, arm	++	+
				Motor, leg	++	+
				Sensory, leg	++	−
				Sensory, arm	++	−
20	61	M	Hypertensive heart disease for 3 yr.; spinal fluid normal; congestive failure present; histamine begun on 2d day, given for 6 days	Mental	++	−
				Motor, arm	++	−
				Motor, leg	+++	+
				Sensory, leg	+	−
21	73	F	Two transient similar episodes 12 and 4 mo. before; spinal fluid normal except for protein of 100 mg./100 cc.; histamine begun on 1st day, given for 8 days	Visual field	+++	−
				Sensory, arm	++	−
				Sensory, leg	++	−
				Motor, arm	+	−
				Motor, leg	+	−
22	65	M	Hypertension for 2 yr.; histamine begun on 2d day, given for 12 days	Speech, motor	+++	−
				Motor, arm	++	−
				Motor, leg	+	−
				Sensory, arm	++	+
				Sensory, leg	++	−
23	57	F	Hypertension for 12 yr.; spinal fluid normal; histamine begun on 2d day, given for 3 days	Motor, arm	+++	−
				Motor, leg	+++	−
				Sensory, arm	++	−
				Sensory, leg	++	−
24	67	M	Hypertension present; transient aphasia 6 mo. before; spinal fluid normal; congestive failure present; histamine begun on 1st day, given for 20 days	Mental	++	−
				Motor, arm	+++	++
				Motor, leg	++	−
				Sensory, arm	++	−
				Sensory, leg	++	−
25	46	M	Dizziness for 3 wk.; hypertension for 20 yr.; histamine begun on 3d day, given for 9 days	Vestibular	++	−
				Motor, bulbar	++	−
				Motor, eyes	++	−
				Sensory, face	++	−
				Coordination leg	++	+
				and arm	++	+
26	58	M	Histamine begun on 1st day, given for 15 days	Speech, motor	+++	+
				Speech, auditory	+++	−
				Speech, writing	+++	+
				Speech, reading	+++	−
27	50	F	Coronary occlusion and transient hemiparesis 1 yr. before; admission for 2d coronary attack; spinal fluid normal except a pressure of 260 mm. of water; histamine begun on 1st day, given for 5 days; death 1 wk. later, of 3d coronary attack	Mental	++	−
				Motor, eyes	++	−
				Motor, leg	++	−
				Sensory, arm	++	−
				Speech, motor	++	−
				Visual field	+++	−
28	81	M	Dizziness for 2 wk.; spinal fluid normal; histamine begun on 1st day, given for 11 days	Mental	+++	−
				Motor, arm	+++	+
				Motor, leg	++	−
				Sensory, arm	++	+
				Sensory, leg	++	−
				Vestibular	++	−
29	57	M	Hypertension for 4 yr.; histamine begun on 1st day, given for 7 days	Mental	+	−
				Motor, arm	+++	−
				Motor, bulbar	++	−
				Speech, sensory	+++	−
				Speech, motor	+++	+
				Speech, written	+++	++
30	57	M	Hypertensive heart disease for 5 yr.; mild congestive failure; spinal fluid normal; histamine began on 3d day and given for 18 days	Speech, motor	+++	+
				Speech, sensory	+++	−
				Motor, arm	+++	+
				Motor, leg	+++	+
				Sensory, arm	++	+
				Sensory, leg	++	−

TABLE 1.—*Clinical Data in Fifty Cases*—Continued

Case No.	Age	Sex	Pertinent Data	Neurological Dysfunction		
				Field Involved	Before	After
			Group 2			
31	54	M	Angina for 2 yr.; right focal seizures for 1 yr.; spinal fluid and skull x-rays normal; histamine begun on 3d day, given for 9 days; occlusion of left anterior cerebral artery shown in arteriogram	Mental	+	—
				Motor, leg	++	+
				Sensory, leg	+	+
				Speech, motor	++	+
				Speech, written	+++	++
32	65	F	Histamine begun 1 mo. after onset of hemiplegia, given for 10 days	Motor, bulbar	++	+
				Motor, arm	+++	++
				Motor, leg	++	+
				Sensory, arm	+	—
				Sensory, leg	+	—
33	54	M	Hypertension present; spinal fluid normal; histamine begun on 1st day, given for 18 days	Mental	+	—
				Motor, arm	+++	+++
				Motor, leg	+++	+
				Sensory, arm	++	—
				Sensory, leg	++	—
34	88	M	Spinal fluid normal; histamine begun on 2d day, given for 12 days	Mental	++	+
				Motor, eyes	++	—
				Motor, arm	++	—
				Motor, leg	+++	—
				Visual field	+++	+++
35	54	M	Hypertension for 10 yr.; spinal fluid normal; histamine begun on 1st day, given for 20 days	Mental	++	—
				Motor, arm	+++	+++
				Motor, leg	++	+
				Sensory, arm	++	++
				Sensory, leg	++	+
				Motor, bulbar	+	—
36	53	M	Hypertension for 15 yr.; coronary occlusion 4 yr. before; spinal fluid normal; histamine begun on 3d day, given for 6 days	Motor, eyes	++	—
				Vestibular	++	—
				Motor, bulbar	++	—
				Sensory, face	++	+
				Sensory, arm	++	++
				Sensory, leg	++	++
				Coordination, arm	++	—
37	32	M	Anaphylactoid reaction to an injection of procaine; spinal fluid normal; histamine begun on 1st day, given for 22 days	Mental	+	—
				Sensory, arm	+++	++
				Sensory, leg	+++	++
				Motor, arm	++	+
				Motor, leg	++	+
				Motor, bulbar	++	+
				Vision, left eye	++	+
38	57	M	Defective walking, speech, and orientation for 5 yr.; pseudobulbar syndrome for 1 yr.; spinal fluid normal except for pressure of 280 mm. of water; histamine begun on 1st day, given for 19 days	Mental	++	+
				Motor, bulbar	++	+
				Motor, arm	+++	+++
				Motor, leg	+++	+++
				Sensory, arm	++	—
				Sensory, leg	++	—
				Visual field	+++	—
			Group 3			
39	75	M	Numbness in leg for 6 wk.; histamine begun on 4th day, given for 13 days, with transient improvement; death on 20th day, in coma	Mental	+++	Died
				Motor, arm	++	
				Motor, leg	+++	
				Motor, bulbar	+	
40	77	M	Spinal fluid normal except for pressure of 280 mm. of water; congestive heart failure; histamine begun on 4th day, given for 5 days; death on 12th day, of heart failure	Mental	+++	Died
				Motor, arm	+++	
				Motor, leg	+++	
				Sensory, head	++	
41	64	M	Five previous strokes; vegetating for 5 mo.; spinal fluid normal; hypertension and heart failure present; histamine begun on 4th day, given for 6 days; death on 11th day; autopsy showed multiple encephalomalacia	Mental	+++	Died
				Motor, arm	+++	
				Motor, leg	+++	
				Sensory, arm	++	
				Sensory, leg	++	
42	67	M	Hypertension for 6 yr.; confusion and pseudobulbar palsy for 4 mo.; spinal fluid normal; histamine begun on 3d day, given for 14 days	Mental	+++	++
				Motor, eyes	++	—
				Motor, arm	+++	+++
				Motor, leg	+++	+++
				Motor, bulbar	++	++

TABLE 1.—*Clinical Data in Fifty Cases*—Continued

Case No.	Age	Sex	Pertinent Data	Neurological Dysfunction		
				Field Involved	Before	After
43	78	F	Two previous bouts of ischemia 3 and 5 yr. before; spinal fluid normal; heart failure; histamine begun on 2d day, given for 3 days; death on 16th day, of heart failure	Mental	++	Died
				Motor, arm	+++	
				Motor, leg	+++	
				Motor, bulbar	++	
				Sensory, arm	++	
				Sensory, leg	++	
44	58	F	Hypertension; congestive failure; spinal fluid normal; histamine begun on 3d day, given for 4 days	Mental	++	—
				Motor, arm	+++	+++
				Motor, leg	+++	+++
				Sensory, arm	++	++
				Sensory, leg	++	++
				Visual field	++	++
45	80	M	Angina and hypertension present; onset with congestive heart failure; spinal fluid normal; histamine begun on 1st day and given for 5 days; death on 6th day, of heart failure and pneumonia	Mental	++	Died
				Motor, arm	+++	
				Motor, leg	+++	
				Speech, motor	+++	
				Speech, auditory	+++	
46	61	M	Transient hemiplegia 1 mo. before; spinal fluid normal; histamine begun on 3d day, given for 24 days, with transient improvement; death on 27th day	Mental	+++	Died
				Motor, arm	+++	
				Motor, leg	+++	
				Sensory, arm	++	
				Sensory, leg	++	
47	83	F	Diabetes poorly controlled; hypertension; blood sugar 362 mg./100 cc.; and blood carbon dioxide 50 vol. %; congestive heart failure; histamine begun on 1st day, given for 5 days; death on 6th day of pneumonia and heart failure	Mental	+++	++
				Speech, motor	+++	
				Speech, auditory	+++	Died
				Motor, arm	+++	
				Motor, leg	+++	
				Motor, bulbar	++	
48	62	F	Spinal fluid normal; histamine begun on 1st day, given for 22 days	Visual field	+++	—
				Speech, motor	+++	+++
				Speech, auditory	+++	+++
				Motor, arm	+++	+++
				Motor, leg	+++	+++
				Sensory, arm	++	++
				Sensory, leg	++	++
49	82	F	Transient azotemia and oliguria on admission for auricular fibrillation and ischemia; histamine begun on 7th day, given for 9 days	Mental	+++	—
				Speech, motor	+++	+++
				Speech, auditory	+++	+++
				Motor, arm	+++	+++
				Motor, leg	+++	+++
				Sensory, arm	++	++
				Sensory, leg	++	++
50	76	F	Vegetating for 2 mo.; congestive heart failure; histamine given for 11 days, from 2d through 5th, and 12th through 20th days	Mental	++	—
				Motor, arm	+++	+++
				Motor, leg	+++	+++
				Sensory, arm	+++	+++
				Sensory, leg	+++	+++
				Speech, motor	+++	+++
				Speech, auditory	+++	+++

marked improvement (Group 1). Eight who showed a reduction of dysfunction ranging from 40 to 66% were designated as showing moderate improvement (Group 2). The 12 remaining patients, who showed less than 20% reduction of dysfunction, were designated as not showing significant improvement (Group 3). Thus, for these 50 patients it can be stated that 76% showed more than 40% improvement, and 60% over 75% improvement.

Among the 12 patients with no improvement there were 7 deaths, 5 from heart failure and 2 from failure of the brain. Two other patients died from the last of a series of coronary thromboses during the hospital admission in which they had been treated for cerebral embolism with histamine. Both had recovered very well from their cerebral ischemia at the time of their deaths. We have included them in the group showing improvement, since it was the effectiveness of therapy in relation

to the lesions in the nervous system that was being evaluated. If these two patients were included in Group 3, the improvement rates would be lowered 4%.

The important data in each case are presented in Table 1. Cases 1 through 30 are in Group 1; Cases 31 through 38, in Group 2, and Cases 39 through 50, in Group 3, arranged according to units of dysfunction in each group.

ANALYSIS OF RESULTS

An analysis of the cases as to the characteristics which may have influenced the response to therapy showed the following factors to have been important: (1) degree of initial neurological dysfunction; (2) presence of bilateral involvement as evidenced by stupor or coma; (3) presence of cardiac insufficiency; (4) age of the patient; (5) day of illness the therapy was begun.

TABLE 2.—*Distribution of Units of Dysfunction in Relation to Therapeutic Responses*

	Groups						
	1		2		3		
Units of Dysfunction at Onset of Therapy	No. of Cases	%	No. of Cases	%	No. of Cases	%	Total
3	1		0		0		
4	3		0		0		
5	5		0		0		
5	5	100	0	0	0	0	20
6	4		0		0		
7	2		0		0		
8	5		0		0		
9	1		2		1		
10	2		0		0		
11	1	44	1	31	1	25	16
12	2		1		0		
13	1		1		2		
14	1		1		3		
15	1	27	0	27	1	46	11
16	1		0		0		
17	0		2		1		
18	0		0		0		
19	0	0	0	0	2	100	3
20	0		0		1		
Total	30 (60%)		8 (16%)		12 (24%)		

Degree of Dysfunction.—Table 2 summarizes the distribution of the units of dysfunction in relation to the therapeutic responses. From the data in Table 1 it is evident that the degree of dysfunction was an important factor in determining whether patients showed marked improvement or no improvement. Of the 20 patients with 8 units or less of dysfunction, all were in Group 1. Of the 14 patients with 14 units or more of dysfunction, only 3 (21%) were in Group 1, as compared with 8 (57%) in Group 3. The distribution of dysfunction is also reflected in the average dysfunction of 8 units for Group 1 and 15 units for Group 3.

The distribution of dysfunction in Group 2 resembled the distribution in Group 3, averaging 13 units of dysfunction; other factors, such as age and the presence of circulatory failure, account for the differences in responses of the two groups.

Evidence of Bilateral Involvement.—A corollary of the degree of dysfunction is the presence of stupor or coma. When the cerebration of the patient is greatly depressed, it can ordinarily be taken as a sign of bilateral cerebral dysfunction, and thus of diffuse ischemia of the brain. Of the 23 patients who were stuporous or

comatose before therapy, 52% showed improvement. It is particularly significant, however, that of the 12 patients in Group 3, with no improvement, 11 (92%) had stupor or coma, three times the incidence for the patients showing improvement.

We believe that stupor or coma frequently indicates that the patient has had, or is having, failure of the systemic circulation which has resulted in the diffuse ischemia of the brain. Clinical evidence of cardiac insufficiency was still present in 55% of the patients with stupor and coma when treatment was begun, emphasizing the importance of careful evaluation of the general circulation in all cases of ischemia of the brain. A history of generalized weakness and decreased tolerance of exercise preceding the bout of cerebral ischemia could be elicited in other cases. That such symptoms indicate a failing circulation has been shown by the prolonged circulation time, commonly doubled, before the usual signs of congestive heart failure are evident.[2]

Of the entire series of 50 patients, 18 had clinical evidence of cardiac insufficiency, of whom 55% showed improvement. Again, it is significant that of the 12 patients in Group 3, without improvement, 8, or 67%, had cardiac insufficiency, 2½ times the incidence in the groups with improvement.

Age.—The distribution of cases according to age is summarized in Table 3.

TABLE 3.—*Distribution of Patients According to Age*

	Ages of Patients					
Group	80's	70's	60's	50's	40's	30's
1	2	10	8	7	3	0
2	1	0	1	5	0	1
3	3	4	4	1	0	0
Total	6	14	13	13	3	1
Per cent improved	50	71	69	92	100	100

Old age itself did not preclude improvement, as evidenced by the fact that of the 20 patients over 70 years of age 12 improved markedly. This was due primarily, we feel, to the low degree of dysfunction (ranging 3 through 8 units) in these patients. A more pertinent indication of the influence of age can be secured from the comparison of patients with similar degree of involvement, ranging 9 through 17 units. Of the 10 patients over 70 years of age in this range of dysfunction, only 3 (30%) showed improvement. On the other end of the age scale, there were 13 patients under 60 years of age in this range of dysfunction, and 12 (92%) improved. The restricted ability of the aged person's circulation to compensate for ischemia of the brain evidently contributes to the severity of the ischemia. When the ischemia has not been severe, even a 70-year-old patient can expect improvement. On the other hand, when the ischemia is profound, the outlook for the septuagenarian is not bright.

Duration of Illness.—The duration of illness before histamine therapy did not vary much in the groups as a whole, as evidenced by Table 4. However, when

2. Blumgart, H. L., and Weiss, S.: Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Arteriosclerosis and in Patients with Arterial Hypertension, J. Clin. Invest. **4**:173 (June) 1927.

patients with similar degrees of dysfunction, 9 through 17 units, are compared, a trend is seen to be present in that 60% of patients in Group 1 were treated on the first day of illness, as compared with 20% in Group 3. Early treatment, thus, may have had significant influence in the severer cases.

PRINCIPLES OF THERAPY

The use of histamine in treatment of ischemia of the brain is based on the following premises:

1. Deficiencies in the circulation of the brain can produce focal and generalized stagnant anoxia of the brain.

2. The anoxia results in a gradient of changes in the brain; whether the neurones remain in a reversible stage of dysfunction is most important.

3. One of the important physiological reactions to anoxia is dilatation of the capillary bed. This defense measure increases the collateral circulation and exposes a larger area of blood, with its vital oxygen, to the brain tissues.

4. Unfortunately, nature's automatic defenses against anoxia are usually inadequate in the extent and duration of the vasodilatation.

5. To supplement and prolong these defenses, intravenous use of histamine given according to the threshold technique can produce a sustained, easily controlled

TABLE 4.—*Duration of Illness Prior to Therapy*

	Day of Illness Therapy Begun				
Group	1	2	3	4	Other
1	12	5	7	2	5th, 6th, 8th, 8th
2	4	1	2	0	30th
3	3	2	3	3	7th

physiological dilatation of the capillary bed, without changes in the blood pressure or undesirable side-effects. The primary and collateral circulation is thus increased in the ischemic areas.

TYPES OF ANOXIA

A deficient blood supply technically produces deficiencies in all the functions of the blood. However, since oxygen lack stops the machine before other deficiencies become significant, the problem of ischemia is primarily one of anoxia.[3] According to Barcroft's classification, the type of anoxia present in ischemia of the brain is the stagnant type, i. e., a condition in which the oxygen saturation of the arterial blood is normal but the blood does not reach the brain, owing to local impediments in the blood vessel (thrombosis, sclerosis, vasospasm) or to failure of the systemic circulation (heart failure, shock). In some cases a combination of the two types of stagnant anoxia, focal and generalized, occurs. If pulmonary edema results from the cardiac insufficiency, a degree of anoxic anoxia is added, owing to the imperfect saturation of the blood passing through the alveoli.[3]

3. Barcroft, J.: Anoxæmia, Lancet **2**:485 (Sept. 4) 1920.

The mechanisms of compensation in stagnant anoxia are different from those in anoxic anoxia.[4] The increase of the minute output of the heart is important in anoxic anoxia in compensating for the low oxygen saturation of the arterial blood. In contrast, the general circulation does not change in focal stagnant anoxia and is actually failing in generalized stagnant anoxia. An increase in the volume of air breathed is one of the main mechanisms of compensation in anoxic anoxia, and oxygen inhalation is very helpful. In stagnant anoxia such mechanisms are of little importance unless pulmonary edema is present.[4c] Vasodilatation and extraction of more oxygen from the blood are the primary mechanisms of compensation in stagnant anoxia and will be discussed in detail below.[4c] It is thus important that the type of anoxia present be correctly diagnosed and treatment adjusted accordingly.

GRADIENTS OF ISCHEMIA

Pathological studies by many investigators[5] has shown in areas of absolute ischemia (Grade 4) that all brain tissue dies and liquefaction necrosis occurs, with cyst formation to follow. In areas of less intense ischemia (Grade 3) the glia and connective tissue survive, but the neurones are destroyed. Such a sparing of tissue does not differ so far as neurological function is concerned, but potential benefit is obtained for collateral circulation in the remaining blood vessels and their anastomoses. In the next degree of ischemia (Grade 2) neurones survive but show reversible histological changes, such as chromatolysis, acute swelling, and vacuolation. In the least degree of ischemia (Grade 1) cells show no histological changes, but their inactivity must be attributed to biophysical changes that cannot be demonstrated in material after death. The best means we have of observing these biophysical changes is in the electrocorticogram and electroencephalogram, but these instruments have limitations also.[6] Therapy, of necessity, is applicable to the ischemias of Grade 1 and 2, and to a degree of Grade 3.

The neurones themselves vary in their thresholds for irreversible changes, the cerebral cortex being most susceptible to anoxia, followed by the cerebellar cortex, the basal ganglia, and the medulla.[5] Although the cells of the medulla are resistant to irreversible changes, in some persons the respiratory center of the medulla is almost as sensitive as the cerebral cortex, and failure of respiratory centers rapidly adds anoxic anoxia, with death from myocardial failure occurring in about 10 minutes.[4a,b] Exhaustion of the respiratory center is considered the principal

4. (*a*) Van Liere, E. J.: Anoxia: Its Effect on the Body, Chicago, University of Chicago Press, 1942. (*b*) Armstrong, H. G.: Principles and Practices of Aviation Medicine, Baltimore, Williams & Wilkins Company, 1951, Chap. 13. (*c*) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Ed. 5, Baltimore, Williams & Wilkins Company, 1950, Chaps. 28 and 35.

5. Evans, J. P., and McEachern, D.: Circulation Changes in Cerebral Vascular Occlusion and in Cerebral Cicatrization, A. Res. Nerv. & Ment. Dis., Proc. (1932) **18**:379, 1938. Weinberger, L. W.; Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation to the Central Nervous System, Arch. Neurol. & Psychiat. **43**:615 (April); 961 (May) 1940. Gildea, E. F., and Cobb, S.: Effects of Anemia on the Cerebral Cortex of the Cat, ibid. **23**:876 (May) 1930.

6. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558 (Nov.) 1938. Harvey, J., and Rasmussen, T.: Electroencephalographic Changes Associated with Experimental Temporary Focal Cerebral Anemia, Electroencephalog. & Clin. Neurophysiol. **3**:341 (Aug.) 1951.

mechanism of sudden death in the anoxic anoxia of aviators and is a constant threat in severe generalized stagnant anoxia or focal medullary ischemia.

In about half the people the cardiac muscle is more sensitive to anoxia than the cerebral cortex. Instead of the gradual dissolution of cerebral function occurring as the cerebral cortex succumbs to anoxia, there is an acute cardiac decompensation, with sudden onset of coma as the blood pressure drops and cardiac output is precipitously decreased. Death can be but minutes away.[4a]

The reactions mentioned above probably account for much of the variation seen in persons in their susceptibility to anoxia. Some healthy young men lose consciousness, and others have died with an arterial oxygen saturation of 70%. In contrast, some persons are alert with an arterial oxygen saturation of 22%.[7] For most people an arterial oxygen saturation of 45% can be fatal after one-half hour.[4a,b] Amid such variation, a useful criterion is Barcroft's evaluation that as long as consciousness is not lost generalized anoxia will not produce irreversible changes except in elderly people.[3] As mentioned above, stupor and coma were present in 92% of the patients with no improvement, a finding which correlates well with this criterion that persistent unconsciousness is a valuable end-point in distinguishing between reversibility and irreversibility and signifies that severe ischemia has occurred.

The damage anoxia produces is dependent not only on the degree of oxygen deficit but also on its duration. The effects of anoxia are cumulative.[4] A man may be conscious at an arterial oxygen saturation of 22%, but will lose consciousness in 1½ to 2 minutes and could die at any time after 20 to 30 minutes.[4] Once the critical level of anoxia has been reached, remedial measures are of no avail. Prompt diagnosis and treatment are very important in limiting the damage of anoxia. Probably in many of our cases a mild degree of dysfunction would have progressed to a severe degree of ischemia if treatment had not been instituted early.

COMPENSATIONS IN STAGNANT ANOXIA

In the final analysis, it is the capillary bed that provides the blood supply to any tissue. Each tissue has developed mechanisms peculiar to its function to modify the blood supply for its own needs. Owing to the restrictions the skull places on increasing the total blood volume in the brain at any one time, vasodilatation and extraction of more oxygen from the blood are the chief methods used by the brain to secure a greater oxygen supply.[4c]

In focal stagnant anoxia the slowing of the blood stream accomplishes automatically the compensatory process of increasing the coefficient of oxygen utilization, more oxygen being removed from the slower-moving column of red blood cells. This mechanism could theoretically compensate almost for a trebling of the capillary circulation time; i. e., if 6.7 vol. % of oxygen is removed from each 100 cc. of blood during each capillary circulation time, the total oxygen load of the blood per 100 cc., 19 vol. %, will last 2.8 circulation times. However, after a delay of twice the normal capillary circulation time and the extraction of 13.4 vol. % of oxygen, the remaining 5.6 vol. % would not sustain function long, if at all.[4] Thus, this mechanism can compensate adequately for a slowing up of the blood flow of only twice the usual capillary circulation time, other aspects of the circulation being constant.

7. Schneider, E. C., and Truesdell, D.: A Study of Low Oxygen Effects During Rebreathing, Am. J. Physiol. **55**:223 (March) 1921.

Vasodilatation of the capillary bed accomplishes two main functions: First, it increases the capacity of the primary circulation to hold more blood, and thus expose more blood to the tissues for transfer of oxygen; second it increases the collateral pathways to circumvent any impediments in the arterial or arteriolar part of the circulation.[4c]

Local ischemia will produce vasodilatation by accumulation of acid metabolites, primarily carbon dioxide and lactic acid.[4] How long this process continues depends on the production of these metabolites and their accumulation due to a defective removal rate. If an area of cells succumbs to anoxia and ceases functioning, though still in a reversible stage, oxygen consumption and carbon-dioxide production will diminish, and eventually the local vasodilator mechanisms will no longer operate. The effects of anoxia will soon then become irreversible. In local ischemia there is no special stimulus for the capillaries neighboring the area of anoxia to dilate and make the normal collateral circulation more effective. For this reason, a continuous, generalized vasodilator would be desirable.[8] In our series the best results were in the cases of focal ischemia.

Generalized stagnant anoxia will produce a generalized vasodilatation of the capillary bed of the brain, but the inadequacies of the systemic circulation outweigh this benefit.[9] Correction of the causes of the circulatory insufficiency is paramount if feasible. In order that the benefits of vasodilatation may be secured, the primary or collateral circulation has to provide the extra blood to the ischemic areas, and without it compensation can only be limited. This was demonstrated in our series in the high incidence (67%) of generalized stagnant anoxia in the patients showing no improvement to a degree that commonly resulted in death from circulatory failure.

The arteriolar network of the pia is very important in compensating for obstructions of the large arterial branches. When obstructions are distal to the pial arterioles, the capillary network has to bear the brunt of accomplishing the shift of blood flow.[9] Theoretically, blood cells could traverse the contiguous capillary bed from one end of the brain to the other,[8] but the time factor plays the same role that it does in limiting the effect of increasing the coefficient of oxygen utilization. Any distance traversed requires time, and oxygen diffuses into the tissues during any time spent in the capillary bed.[4c] A more rapid transit through the capillary bed is permitted, with less resistance from the dilatation of the vessels, as long as the arterial pressure head is maintained. For example, in maximum dilatation in the skin capillaries, blood can traverse the capillary bed so rapidly that the venous blood has practically the same oxygen saturation as the arterial blood.[4c] The advantage of similar changes in capillary flow in anoxic areas is obvious.

Just how deep from the fringes of an ischemic area the collateral circulation can penetrate is not known. We have observed that clinical recovery, as it appeared, was usually along the estimated fringes of the ischemic area. The major arteries, nevertheless, have often an area of absolute ischemia that collateral circulation does not seem to reach adequately. Thus, the larger the area of ischemia, the less the probability of any considerable improvement. On the contrary, smaller areas of ischemia would be more easily penetrated by the collateral circulation. We believe

8. Cobb, S.: Cerebral Circulation, A. Res. Nerv. & Ment. Dis., Proc. (1937) **18**:719- 1938.

9. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Res. Nerv. & Ment. Dis., Proc. (1937) **18**:471, 1938.

that this explains much of why the degree of dysfunction correlates so highly with the degree of improvement in our cases.

The capillary system of the brain, hidden within the skull, still evades one's best efforts to measure consistently changes in its blood flow qualitatively, or, even more so, quantitatively. The capillary flow may vary directly or inversely with the extracranial flow and with variable ratios. In fact, the capillary flow commonly is modified without changes in the extracranial flow.[9c] Dilatation of a capillary may increase the velocity of the blood by reducing the resistance in it; but with a simultaneous increase in the cross-sectional area of the capillary the blood flow tends to be slowed.[9c] With so many variables it is not practical to use the extracranial blood flow to measure capillary flow. One still has to rely on direct observations of the capillary bed in experimental animals and use the data inferentially in clinical work, with appropriate reservations.

HISTAMINE AS A VASODILATOR

Histamine is one of the physiological vasodilators found throughout the animal kingdom.[10] There is a wide species sensitivity, from the cat, with the greatest sensitivity, to the rabbit, which is a thousand times less sensitive. Man is one of the more sensitive animals.[11] Histamine is normally present in the blood of man at a concentration of 0.03 to 0.04 γ per cubic centimeter.[11] It has been found in extracts of all living tissues studied.[10] It is produced during active contraction of skeletal and smooth muscles and of the heart and is considered to be responsible for the local increase of blood flow in these organs during activity.[12] Histamine is inactivated rapidly by the enzyme histaminase, which is also found in all living tissues.

Histamine has two primary actions: (*a*) dilatation of the capillary bed of tissues, and (*b*) stimulation of the smooth muscle of the large arteries, bronchioles, intestine, and heart. These actions are modulated according to the concentration of histamine in the blood, for there is a definite order of tissue sensitivity, as well as graded individual responses.

Small continuous intravenous doses in man can preferentially dilate the capillaries of the skin and brain, but not of the viscera.[13] There is enough compensatory increase in cardiac output to prevent any change in blood pressures.[14] With such a threshold dosage there is no stimulation of the bronchioles or the intestine. This effect is secured with an administration of 0.006 to 0.02 mg. per minute. We have

10. Sollmann, T.: A Manual of Pharmacology, Ed. 7, Philadelphia, W. B. Saunders Company, 1948, p. 406.

11. Barsoum, G. S., and Gaddum, J. H.: Pharmacological Estimation of Adenosine and Histamine in the Blood, J. Physiol. **85**:1 (Aug.) 1935.

12. (*a*) Anrep, G. V., and Barsoum, G. S.: Appearance of Histamine in the Venous Blood During Muscular Contraction, J. Physiol. **85**:409 (Nov.) 1935. (*b*) Anrep, G. V., and von Saalfeld, E.: Blood Flow Through the Skeletal Muscle in Relation to Its Contraction, ibid. **85**:375 (Nov.) 1935. (*c*) Barsoum, G. S., and Gaddum, J. H.: Liberation of Histamine During Reactive Hyperemia, ibid. **85**:13 (July) 1935.

13. Weiss, S.; Robb, G. P., and Ellis, L. B.: Systemic Effects of Histamine in Man with Special Reference to Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (March) 1932.

14. Grollman, A.: Cardiac Output of Man in Health and Disease, Baltimore, Charles C Thomas, Publisher, 1932, p. 184.

found that persons with low threshold will react with gastrointestinal symptoms at triple their threshold dose. We have not encountered bronchiolar constriction in any of the subjects, even with an accidental overdose in one case (5.5 mg. of the phosphate was injected into the tubing, instead of the flask of 1,000 cc.) that produced transient circulatory collapse, an observation indicating that the smooth muscle of the bronchioles is the least sensitive to histamine in man.

The heart is mildly stimulated by histamine in the minimal effective concentrations and results in an increase of the pulse rate and an increased cardiac output.[14] This increase in pulse rate or the facial flush should be used as the end-point of histamine administration, and not the change in blood pressure, which has been used in several studies on cerebral blood flow. Reduction in the blood pressure will diminish the effectiveness of the vasodilatation, but this is easily avoided, since the decrease begins to occur at a dose of 0.08 mg. per minute, 4 to 13 times the recommended therapeutic concentrations.[13] It is as undesirable to use the blood-pressure changes as an index of vasodilatation with histamine as it would be to use hypoglycemic reactions as the index of effectiveness of insulin in diabetes.

An important feature of histamine is its safety in physiological doses. The body is accustomed to handling histamine, for, as mentioned above, it is being constantly produced by the activity of smooth muscle, the heart, and skeletal muscle.[12] Vigorous skeletal-muscle contraction can increase the histamine level in the blood tenfold, which, in turn, produces a marked vasodilatation in the muscles and skin. This effect subsides in about 10 minutes, an interval about the same as that following the cessation of the intravenous infusion of histamine. Thus, the administration of histamine is analogous to the use of other naturally occurring substances, such as epinephrine and insulin. As with them, precise dosage brings predictable, physiological reactions.

Whether histamine is ordinarily produced in ischemia of the brain has not been determined. Anoxia to a limb, by transient occlusion or venous shunt, is known to increase the blood histamine from that limb two to four times in dogs.[12] Since histamine is formed by the decarboxylation of histidine by acids, the acid metabolites, lactic acid and carbon dioxide, found in anoxia could well instigate this reaction.[12] Breathing 10% carbon dioxide and 20% oxygen produced a doubling of the blood histamine level and raises the question whether the vasodilator effect of carbon dioxide is mediated through histamine.[12c] Whether the brain uses a system similar to that in the muscles is a point physiologists need to investigate further. Current opinion is that the acid metabolites directly produce the vasodilatation in the brain during anoxia.[4]

SCHEDULE OF HISTAMINE THERAPY

The regimen of histamine therapy we have evolved involves the diagnosis of the presence of ischemia and the institution of treatment as early as possible. A spinal fluid examination was usually needed to differentiate severe ischemia from gross cerebral hemorrhage and cerebral edema. We excluded all cases with a spinal fluid pressure over 300 mm. of water. The vehicle for the histamine usually used was 5% dextrose in saline. The dextrose was omitted in cases of diabetes and the saline in cases of hypertension if the patient was under salt-restriction therapy. The concentration of histamine we found easiest to work with was 5.5 mg. of the phosphate

in 1,000 cc. of the vehicle. With a standard drip regulator, the rate of administration was begun at 20 drops per minute. This will produce satisfactory vasodilatation in the most sensitive patients. If no facial flush was observed in two to three minutes, the speed was increased in steps of 5 to 10 drops, with a few minutes of observation between increases. The correct speed was noted for future infusions, as it was relatively constant in the same subject. Seldom was 80 drops per minute exceeded. In cases in which fluid needed to be restricted, the volume of the vehicle was reduced to 500 or 250 cc., with a proportional decrease in the speed of administration.

Once the diagnosis of ischemia of the brain was established, an infusion was given for four to six hours and repeated twice daily until improvement had been maintained for two or three days. We have usually made a two-week trial of histamine therapy before giving up a patient as unimproved. Nicotinic acid, 50 to 100 mg. every three hours between infusions, was given in the hospital if feasible and its administration continued after discharge.

COMMENT

In the investigation of any therapy the pertinent question is whether the incidence of change is significantly more than that in a control group. The difficulty in answering this specifically is the problem of getting similar study and control groups. For example, in the first series of 25 patients treated with histamine,[1] pronounced neurological dysfunction, coma, cardiac failure, and ages over 70 were infrequent. In the present series these factors were common. Since such factors diminish the recovery rate, the response to therapy will be inversely proportional to their occurrence. This is borne out in a comparison of the improvement rates of 92 and 76% for the two series. We believe that, allowing due credit to nature's disaster corps, the use of histamine at least doubles the incidence of improvement in cases of ischemia of the brain and is a step forward in the battle against stagnant anoxia.

SUMMARY AND CONCLUSIONS

Fifty patients with ischemia of the brain were given histamine therapy according to the intravenous threshold technique. The results were evaluated according to a qualitative and a quantitative system of units of dysfunction. Thirty patients were considered to have shown an improvement of over 75% and 8 patients, improvement of 40 to 66%.

The factors which appeared to exert a favorable influence toward improvement were a mild degree of neurological dysfunction, absence of stupor or coma, absence of cardiac insufficiency, an age of under 60, and short duration of dysfunction.

Ischemia may produce a focal and generalized stagnant anoxia, to which the brain reacts with extraction of more oxygen from the blood and vasodilatation in order to increase the primary and collateral circulation.

Histamine is a physiological vasodilator used normally by the body to increase the blood supply to smooth muscles, the heart, and skeletal muscles during increased activity. Histamine can be used safely and effectively in assisting the body to compensate for interference with the blood supply to the brain.

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PROBLEMS RELATED TO TREATMENT OF INTRACRANIAL ANEURYSMS BY CAROTID LIGATION

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THE PURPOSE of carotid ligation in the treatment of intracranial aneurysms is to reduce the pressure and pulsation within the aneurysm so as to decrease the size of the aneurysm and allow thickening of the walls, and thereby to relieve the compression of adjacent structures and to diminish the possibility of rupture. This purpose is not attained, however, if subsequently, through the presence or the development of sufficient collateral circulation, the blood pressure regains its original level while the aneurysm is still present in the same form. Fortunately, in some cases clotting within the aneurysm, as a result of the reduced pressure and subsequent organization and strengthening of the wall of the aneurysm, obliterates or reduces the lumen of the aneurysm. In such a case return of the pressure would be less likely to result in the reexpansion of the aneurysmal sac or in rupture.

Carotid ligation may theoretically lead to one of three different results:

A. Slight or no reduction in blood pressure in the homolateral arterial tree. (The development of collateral circulation through the circle of Willis may reinstate the original pressure.)

B. Permanent reduction in blood pressure and pulse pressure in the ipsilateral arteries and/or thrombosis in the aneurysm. (The chance of further bleeding is thus substantially reduced or eliminated.)

C. The occurrence of complications, such as contralateral abnormal neurological signs or death, caused by hypoxemia consequent to reduced blood flow [1] or by thrombosis of the smaller arteries of the brain or of the internal carotid artery itself, propagating into or shooting emboli into the smaller vessels.[2] In most instances hypoxemia may be assumed to be responsible for the complications, as witnessed by the fact that most complications are reversible by prompt clip removal.[3]

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1. Schorstein, J.: Brit. J. Surg. **28**:50-70, 1940.

2. (*a*) Dandy, W. F.: Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Co., Inc., 1944. (*b*) Perthes, G.: Arch. klin. Chir. **114**:403-415, 1920. (*c*) Voris, H. C.: J. Neurosurg. **8**:119-131, 1951.

3. Brackett, C. E., and Mount, L. A., in Surgical Forum: Proceedings of the Forum Sessions, Thirty-Sixth Clinical Congress of the American College of Surgeons, Boston, October, 1950, Philadelphia, W. B. Saunders Company, 1951, pp. 344-358.

There is no doubt that thrombosis within the aneurysm occurs after carotid ligation in a number of cases. It has been claimed, however, that when a patent circle of Willis exists thrombosis within the aneurysm occurs in those aneurysms originating from the internal carotid artery proximal to the circle of Willis. It was reasoned that collateral circulation distal to the circle of Willis would be so efficient that unilateral carotid ligation would not lead to any appreciable reduction of blood flow or pressure,[4] so that carotid ligation would be inadequate if the aneurysm were located peripheral to the circle of Willis.[5]

There are many arguments against this assumption. For example, patients have been described with aneurysms distal to the circle of Willis in whom the aneurysms after carotid ligation were found to be thrombosed at autopsy,[6] at craniotomy by local palpation and needling of the aneurysm, or by arteriography.[7] To determine directly whether the peripheral circulation of the brain is in any way influenced by carotid ligation, it was decided to record pressures simultaneously in the internal carotid artery and in a small cortical artery on the same side.

RESULTS OF CAROTID LIGATION

CASE 1.—Patient A, a 24-year-old woman, had been healthy prior to the occurrence of proved subarachnoid hemorrhage, one month and, again, three weeks, before admission to the Neurological Institute. At the time of admission the only lateralizing clue in the history was a preponderance of the headache during the bleeding episodes in the right frontal region. The neurological examination revealed only mild weakness of the left lower part of the face. The special studies, including x-ray examinations of the skull, visual field determinations, and electroencephalographic studies, were not helpful in localization. A percutaneous carotid arteriogram, performed on the right side, demonstrated a saccular aneurysm originating from the main trunk of the middle cerebral artery and situated in the Sylvian fissure. On compression of the carotid arteries on the left side, there appeared excellent filling of the arteries on the left side, indicating an efficient collateral circulation through the anterior communicating artery. Carotid arteriography on the left side revealed no further abnormalities. It was decided to approach the aneurysm directly by operation. This was done 5½ weeks after the initial hemorrhage. First, the carotid arteries on the right side were exposed and the common, internal, and external carotid arteries isolated and identified. A polyvinyl resin catheter was introduced into the internal carotid artery through a 21-gauge needle, and it remained in position during the operation. This catheter was connected with the Lilly capacitance manometer to record pressures.[8] Thereafter a right frontotemporal craniotomy was performed, and after the dura was opened, a 26-gauge needle was introduced into a small temporal branch of the middle cerebral artery, with the point directed proximally. A catheter fitted to this needle connected it with a Lilly manometer. It was noted on a first attempt to introduce the needle that a marked spasm of the artery occurred, but a second attempt was completely successful.

Pressure Recordings.—At first the recorded pressure in the internal carotid artery was 114/77, and that in the cortical artery, 78/54; and the pressure stayed at the same levels during a period of 10 minutes. Occlusion by clamping the external carotid artery did not result in any change of these pressures. Occlusion of the right common carotid artery resulted in a prompt fall of pressure at 68/58 in the internal carotid artery (a fall of 34% of the original mean pressure level), and to 51/43 in the cortical artery (a fall of 29% of the original mean pressure level). Additional percutaneous occlusion of the left carotid arteries resulted in a further fall: The mean pressure in the right internal carotid artery showed an additional fall of

4. Albright, F.: Bull. Johns Hopkins Hosp. **44**:215-245, 1929.
5. Poppen, J. L.: J. Neurosurg. **8**:75-102, 1951.
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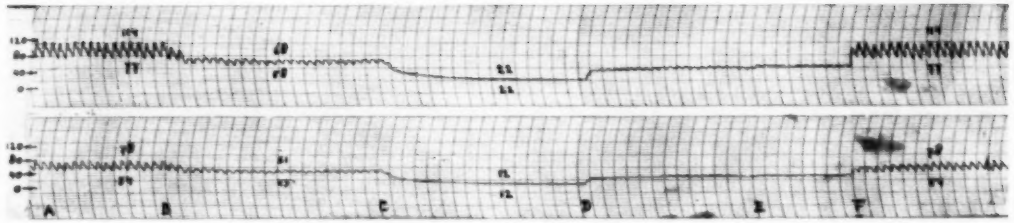

Fig. 1.—The upper curve represents the pressure recordings in the right internal carotid artery.

The lower curve represents the pressure recordings in the right cortical artery, a temporal branch of the middle cerebral artery.

During period *A-B* the right external carotid artery was occluded. *B* marks additional occlusion of the right common carotid artery; *C*, additional occlusion of the left internal carotid artery; *D*, release of the occlusion of the left internal carotid artery; *E*, release of the occlusion of the right external carotid artery; *F*, release of the occlusion of the right common carotid artery.

43% of the original level, and in the cortical artery, one of 53% of its original level (Fig. 1). Removal of the different occlusions in steps reinstated the original pressure.

As this recording indicated that the pressure in the aneurysm would be influenced by carotid ligation, it was decided to limit the operation to a complete ligation of the internal carotid artery and to abandon the attempt to treat the aneurysm locally. A Selverstone clamp was placed around the internal carotid artery and was closed completely the next day, after the patient had regained consciousness and was stabilized. No complications followed this procedure.

In this patient there was, according to arteriographic and pressure studies, a patent collateral circulation. Nevertheless, occlusion of the common and external carotid arteries resulted not only in a fall in blood pressure in the internal carotid artery, but, to an almost equal degree, in a fall in blood pressure in a peripheral cortical artery. It is true that this study did not indicate whether and after how long a time collateral circulation will again establish a normal blood flow in the homolateral hemisphere. Neither is it known, however, how long and to what extent blood flow or pressure has to be reduced to cause thrombosis in an aneurysm, variable as this may be in relation to size, form, and location of the aneurysm. The fact that the blood pressure distal to the circle of Willis, and even far peripherally, is profoundly affected by carotid ligation proves, however, that it is theoretically possible to expect thrombosis in an aneurysm in this part of the circulation, or at least reduction in the pressure and pulsation within the aneurysm.

Case 2.—The same procedure was repeated in a woman (B) aged 42, who had suffered a proved subarachnoid hemorrhage seven months prior to admission to the Neurological Institute. At this time, according to the clinical observations, there had been extension of the bleeding into the left hemisphere, but there were no notable sequelae of this at the time of admission. Bilateral percutaneous carotid arteriography revealed two small aneurysms, one on the right middle cerebral artery prior to its division into branches, and situated in the right Sylvian fissure, and one on the left middle cerebral artery, 2 cm. distal to its origin. With right-sided arteriography and compression of the left internal carotid artery, it was noted that no iodopyracet (diodrast®) passed to the opposite side, nor was the right anterior cerebral artery visualized. With left-sided arteriography both anterior cerebral arteries were demonstrated and seemed to originate from the left side. Hence there was a defect or absence of collateral circulation through the anterior portion of the circle of Willis. As the aneurysm on the left side apparently had been the origin of bleeding, it was decided to perform carotid ligation on the left side. At operation the carotid arteries on the left were exposed and a catheter was inserted into the lumen of the left internal carotid artery. The cortex was subsequently exposed through a small trephine opening over the left temporal lobe, and a 26-gauge needle with attached catheter was introduced into a small cortical artery, with the point directed proximally. The recorded pressure in the internal carotid artery was 120/71; that in the cortical artery, 54/40. Occlusion of the left common carotid artery resulted in a fall to 27/21 in the internal carotid artery (a fall of 75% of the original mean pressure level), and to 17/16 in the cortical artery (a fall of 65% of the original mean pressure level). Additional occlusion of the left external carotid artery or the left jugular vein did not result in any change. Attempts to compress the internal carotid artery on the other side were unreliable, owing to the position of the patient. A Selverstone clamp was placed around the internal carotid artery, as it was believed that the collateral circulation would be reestablished less quickly than when the common carotid artery was ligated. The next day, when the patient was again fully conscious, this clamp was closed completely. Immediately thereafter there were transient weakness and clumsiness of the right hand, which lasted approximately 10 minutes. Three hours after the occlusion the extinction test for pain was transiently positive over the right arm and leg, with a normal subjective sensibility to pain. Six hours after the occlusion weakness of the right arm and slight weakness of the right lower part of the face developed. Shortly thereafter the patient became unresponsive. The clamp was immediately released. The patient regained consciousness at once, and neurological recovery was complete within half an hour. Three days later the patient tolerated occlusion of the internal carotid artery to 1 mm. of complete ligation.

The pressure studies showed deficient collateral circulation, as did arteriography. Occlusion of the common and external carotid arteries resulted in a substantial fall in blood pressure in the internal carotid artery, and to a slightly less degree in the peripheral cortical artery. The fall in blood pressure in this instance far exceeded the fall in the first case, and complications were predicted.

Case 3.—A woman aged 52 had her first subarachnoid hemorrhage in November, 1949. Her second occurred in February, 1950, and with it left hemiplegia developed, which lasted 48 hours. The third occurred in April, 1950, and the fourth occurred the morning after the third. Twenty-six days after the fourth hemorrhage she still had a residual hemiparesis, and at that time, with the patient under the care of Dr. William P. Tice, of Roanoke, Va., an arteriogram was made, demonstrating an aneurysm of the right internal carotid artery at its junction with the posterior communicating artery (Fig. 2*A*). The internal carotid artery was occluded an estimated 70%. Flaccid left hemiplegia developed 20 minutes after the patient had returned to her room. The ligature was removed; a stellate block was performed, and cellophane® was wrapped around the internal carotid artery to produce gradual occlusion by the production of scar tissue. She began to regain the use of the left extremities a few hours later.

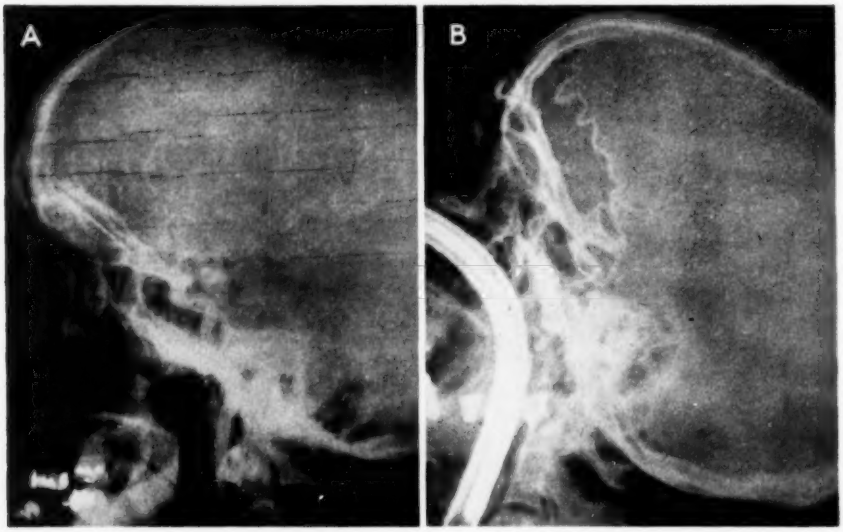

Fig. 2.—*A*, arteriogram revealing an aneurysm of the internal carotid artery; *B*, arteriogram two years after operation, showing no aneurysm, and the diameter of the internal carotid artery less than one-half that before operation.

When first admitted to the Neurological Institute, in April, 1952, she had only slight residual left hemiparesis. A right carotid arteriogram was normal, no aneurysm and no displacement of the arteries being demonstrated (Fig. 2*B*). The internal carotid artery was only about one-half the size it had been two years previously.

In a certain number of patients the results of carotid ligation for the treatment of aneurysms will be favorable, leading to the results mentioned under B. As yet it is not known, however, in how great a percentage of or in which patients this will occur. This is extremely important to know in deciding whether carotid ligation or the direct intracranial approach is the treatment of choice for an intracranial aneurysm. This is especially so because it has been claimed that untreated aneurysms, if once past the immediate dangerous period of two to four weeks following

hemorrhage, may not bleed again for a long time,[9] or may even thrombose spontaneously, and, on the other hand, have been known to bleed again 27 years after the first hemorrhage.[10] Therefore extensive statistical studies are indicated to determine the results of the various methods of therapy. Carotid ligation should be followed at a later date by arteriography to obtain information regarding the results. These studies have been undertaken in the Neurological Institute, and will be published at a later date.

Result A, which leads to a return of the original situation after a while, is harmless to the patient as far as the procedure of carotid ligation is concerned. To improve the results of carotid ligation, it is especially important to decrease the frequency of the immediate postoperative complications, result C. One way of doing this is by using the Selverstone clamp with its tools, by means of which the occlusion can immediately be released if complications arise.[11] The speed with which this is done is essential to the reversibility of the complications.[12] The Selverstone clamp is now used routinely in cases of carotid ligation at the Neurological Institute. An additional advantage of this clamp is that the occlusion may be done in steps if desired.

Another important contribution would be the ability to predict in a given instance the likelihood, or even certainty, of complications. It speaks for itself that this probability is increased with the amount of deficiency of the collateral circulation. The anterior communicating artery has been shown to be deficient in approximately 10% of cases, and the posterior communicating artery, in approximately 23%.[13] There are two ways available in which to determine preoperatively the adequacy of collateral circulation. The first means is by arteriography. To obtain this information, it is necessary to perform a complete bilateral carotid and vertebral arteriographic study, and, moreover, when taking the anteroposterior roentgenograms, to compress the contralateral internal carotid artery when injecting the contrast material, to be able to observe how much of it flows across the midline into the opposite arterial tree.[3] A second method, introduced by Sweet and co-workers,[14] is pressure recordings from the internal carotid artery and the response of the pressure to the occlusion of different arteries. Occlusion of the internal carotid artery or combined occlusion of the common and external carotid arteries resulted in a fall of pressure in the internal carotid artery distal to the occlusion. In a series of 39 cases published by Sweet and co-workers [14] the average fall of the mean pressure was 43% of the original level (or to 57% of the original level). In their series there were three patients in whom the systolic pressure fell 70% or more of the original level. It is not mentioned in these articles how many of the 39 patients underwent carotid ligation, but the only fatal outcome of carotid ligation occurred in one of these 3 patients, while another one of these died after an injection of iodopyracet. These were the only two fatalities in the whole series, and it is thus speculated that the fall of pressure has prognostic implications. If collateral

9. Wolf, G. A.; Goodell, H., and Wolff, H. G.: J. A. M. A. **129**:715-718, 1945. Hyland, H. H.: Arch. Neurol & Psychiat. **63**:61-79, 1950.

10. Rosen, S. R., and Kaufman, W.: Arch. Neurol. & Psychiat. **50**:350-354, 1943.

11. Selverstone, B.: To be published.

12. Sweet, W. H., and Bennett, H. S.: J. Neurosurg. **5**:178-195, 1948. Brackett and Mount.[3]

13. Padget, D.: Cited by Dandy,[2a] Vol. I, pp. 67-90.

14. Sweet, Sarnoff, and Bakay.[6] Sweet and Bennett.[12]

circulation is deficient, the fall in pressure will be greater, and there will be more likelihood of complications developing. With persistence of the occlusion outlined above, Sweet and co-workers then additionally occluded the contralateral internal carotid artery and recorded an average further fall of approximately 30% of the original mean pressure in the ipsilateral internal carotid artery. There was, however, a great variation in actual values, and they concluded that if this second step results in a marked additional fall, the bulk of the collateral circulation goes through the anterior communicating artery. If there is, however, but little additional fall, the basilar artery and the posterior communicating artery must carry the most important part of the collateral supply.[12]

We have tried to determine the condition of the collateral circulation through the circle of Willis both by the arteriographic method and by the method of pressure recording. The number of cases thus collected is 14, in all of which carotid ligation

TABLE 1.—*Data on Fourteen Patients with Carotid Ligation*

Fall in Pressure in Internal Carotid Artery, in Percentages of Original Pressure, After Occlusion of Internal Carotid Artery or Combined Occlusion of Common and External Carotid Arteries			Additional Fall, in Percentages of Original Pressure, with Contralateral Compression Added to Ipsilateral Carotid Occlusion		Filling of the Contralateral Cerebral Arteries upon Arteriography with Contralateral Compression
Systolic Pressure, %	Mean Pressure, %	Diastolic Pressure, %		Mean Pressure, %	
40	34	25	Pat. A	43	Excellent
43	39	33	.....	15	Excellent
49	43	35	Pat. C	?	?
45	45	46	.....	?	Excellent
54	46	32	.....	?	?
54	47	32	.....	25	Excellent
57	49	36	.....	18	?
57	57	57	.....	?	None
64	59	52	.....	9	None
66	62	53	.....	11	None
68	66	60	.....	?	?
71	67	59	Pat. E	11	None
77	75	70	Pat. B	?	None
79	76	71	Pat. D	5	Minimal

was done, and in 4 of which complications occurred but recovery was complete after prompt clip removal (Tables 1 and 2). This series is too small to permit any definite conclusions, but a few interesting points were observed. There were seven patients in whom, after occlusion of the internal carotid artery or of the external and common carotid arteries, the pressure in the internal carotid artery showed a fall of 55% or less of the original mean value. Four of these patients showed a good collateral circulation on arteriography with compression; in the three others no compression was performed. In four of these patients the internal carotid artery was completely ligated; in the other three the common carotid artery was ligated, also completely. In only one of these patients, with a complete ligation of the internal carotid artery, did complications occur.

This patient (C), a woman aged 43, with proved episodes of subarachnoid hemorrhage seven weeks and three weeks prior to operation, was shown to have a saccular aneurysm of the intradural portion of the left internal carotid artery. Complete ligation of the left internal carotid

TABLE 2.—*Complications After Carotid Ligation in Four of a Total of 14 Patients*

Patient	Fall in Pressure in Internal Carotid (in Percentages of Original Pressure) After Occlusion of the Internal Carotid or Combined Occlusion of Common and External Carotid Arteries: Systolic Pressure, %	Fall in Pressure in Internal Carotid (in Percentages of Original Pressure) After Occlusion of the Internal Carotid or Combined Occlusion of Common and External Carotid Arteries: Mean Pressure, %	Additional Fall, in Percentages of the Original Pressure, with Contralateral Compression Added to Ipsilateral Carotid Occlusion; Mean Pressure, %	Filling of Contralateral Cerebral Arteries upon Arteriography with Contralateral Compression	Type of Ligation Performed	Complications After Ligation	Course After Prompt Clip Removal
B	77	75	?	None	Internal carotid, completely	Hemiplegia and coma 6 hr. later	Full recovery in ½ hr.
C	49	43	?	?	Internal carotid, completely	Hemiplegia and aphasia 5 min. later; shortly before this, blood pressure in arm not obtainable by cuff method	Full recovery in 24 hr.; subsequent complete ligation of internal carotid artery 3 wk. later; no complications
D	79	76	5	Minimal	Common carotid, partially	Hemiplegia and coma 1½ hr. later	Generalized convulsions; recovery of consciousness in 50 hr.; full recovery in 4 days
E	71	67	11	None	Common carotid, completely	Hemiplegia, aphasia, confusion, and blindness after 2 hr.	Full recovery in 52 hr.

artery was performed, and approximately five minutes thereafter there developed aphasia and right hemiplegia with Babinski sign. However, immediately before this happened, the anesthetist had noticed that it was impossible to record the blood pressure by cuff, owing to a sudden fall in pressure. The clip was immediately removed; carbon dioxide and oxygen inhalations were administered, and a stellate ganglion block was performed. Within five minutes the blood pressure regained a level of 90/60, and the patient recovered gradually, but completely, over the next 24 hours.

It was thought likely in this patient that the complications were due to the additional burden of a suddenly reduced general blood pressure upon a cerebral blood flow already reduced by carotid ligation. The fall in general blood pressure was probably due to the carotid sinus reflex.[15] Three weeks later the patient was again operated upon. The autonomic nerves were stripped from the wall of the artery, and again a complete occlusion of the internal carotid artery was performed, this time without any ill effects.

This case demonstrates the importance of the behavior of the general blood pressure.

There were three patients in whom the mean pressure in the internal carotid artery after unilateral carotid compression showed a fall of from 55 to 65% of the original mean pressure. These three patients all showed deficient anterior collateral circulation through the circle of Willis upon arteriography with contralateral compression. In one a complete ligation of the internal carotid artery was performed; in one a complete ligation of the common carotid artery was done, while in the third the common carotid artery was only partially occluded, to an estimated 50%. None of these patients suffered from postoperative complications, though one of them showed a contralateral Babinski sign shortly after ligation, which was, however, transient, and in one the ligation was not complete, as mentioned.

There were four patients in whom the mean pressure showed a fall of 65% or more of the original level after unilateral carotid compression. Three of these revealed deficient or absent collateral circulation through the anterior communicating artery on arteriography, while in one no contralateral compression was done during this procedure. In two of these patients complete ligation of the internal carotid artery was performed; in one, complete ligation of the common carotid artery, and in one, partial occlusion of the common carotid artery. In three of these patients complications arose—in one, after complete ligation of the internal carotid artery; in one, after complete ligation of the common carotid artery, and in the third, after partial ligation of the common carotid artery. These three patients were the only ones in this series in whom the systolic pressure fell more than 70% of its original value. The fourth patient, who showed no complications, was the only one in this series of 14 with an arteriovenous angioma in the temporal lobe, instead of an aneurysm, and this probably presents a different relation as regards pressure recordings and cerebral blood flow. The systolic pressure in this patient showed a fall of 68% of its original value. The patient who suffered complications after partial ligation of the common carotid artery presents another problem.

She was a woman aged 48 (Patient D) with proved subarachnoid hemorrhage two months prior to operation, who had a small aneurysm on the junction of the right internal carotid artery and the right posterior communicating artery. Because the pressure recordings in her case seemed to indicate that complete occlusion might be dangerous, as the mean pressure showed a fall of 76% of its original level after occlusion of the common carotid artery, it was decided to proceed with only a partial ligation. The pressure in the right internal carotid artery was 114/65 at the time the clip was placed on the common carotid artery, while her usual blood

15. Thompson, R. K., and Smith, G. W.: Tr. Am. Neurol. A. **76**:203-207, 1951.

pressure was 130/70. The clip then was partially occluded until a pressure of 92/46 was recorded. Thirty minutes later, while the wound was being closed, the pressure in the internal carotid artery had gradually risen to 104/52. One and a half hours after the partial occlusion the patient suddenly complained of spots before her eyes and became unresponsive in a matter of seconds, and left hemiplegia, involving also the facial muscles, was noted. The clip was immediately removed; caffeine intravenously and oxygen by mask were administered, and some improvement followed. Later in the day generalized seizures occurred while the hemiplegia persisted. The patient was treated with sedatives and repeated stellate ganglion blocks bilaterally. She regained consciousness 50 hours after the occlusion, and four days after the operation she had completely recovered, except for minimal weakness of the left arm.

In this instance the blood pressure in the internal carotid artery was only minimally reduced by partial occlusion of the common carotid artery, and nevertheless complications ensued. The remaining pressure was certainly greater than in some of the other patients who showed no complications after complete ligation. This case, then, may be considered as a warning against applying too rigid mechanical theories to the procedure. The arterial system is a dynamic vasomotor system in which the blood flow may be reduced by arteriospasm. This limits the value of pressure recordings in ultimately prophesying complications.

In four of the seven patients who showed a fall in pressure of 55% or less of the original mean pressure upon occlusion of the homolateral internal or external and common carotid arteries there was performed a reliable additional occlusion of the contralateral internal carotid artery. This resulted in a further fall of from 15 to 50% of the original mean pressure. In three of these four patients arteriography indicated a patent collateral circulation through the anterior communicating artery; in the fourth patient no contralateral compression was performed.

In four of the seven patients in whom the mean pressure with the first homolateral occlusion showed a fall of 55% or more of its original level reliable additional compression of the contralateral internal carotid artery resulted in a further fall of less than 15%. These four patients all showed a deficient or absent collateral circulation through the anterior communicating artery by arteriography with contralateral compression.

These data thus seem to support Sweet and Bennett's suggestion [12] that the efficacy of the collateral circulation largely by way of the anterior communicating artery may be checked by pressure recordings in the internal carotid artery after occlusion of the artery proximally and after the additional percutaneous compression of the carotid arteries on the contralateral side. In addition, when both carotid arteries are occluded, the remaining pressure is evidence of collateral circulation from the basilar artery, mostly through the posterior communicating artery. If the remaining pressure is zero, or nearly so, one can assume that the posterior communicating artery is contributing little or nothing to the collateral circulation and can be sacrificed if necessary. The series presented is too small from which to draw definite conclusions, but the following conjectures may be made: Deficient collateral circulation results in occurrence of complications after carotid artery ligation. Evidence of deficiency is suggested by the fall of the blood pressure in the internal carotid artery of more than 65% of the original mean value upon occlusion of the homolateral internal carotid artery or the external and common carotid arteries. It has to be kept in mind, however, that one is dealing with a dynamic vasomotor system and that unpredictable changes may occur through reduction of the general blood pressure [15] of thorough local vasospasm.[2e] Therefore, though pressure record-

ings will give a valuable clue as to the outcome of the ligation, they are not completely reliable. At the same time it must be remembered that, though patients with deficient collateral circulation have a greater chance of complications, they also, because of the marked reduction of pressure, stand a greater chance of having a thrombus develop in the aneurysm after carotid ligation and have less danger of rupture.[16]

More studies are necessary to determine the percentage of patients whose aneurysms, either at the base or peripherally, become thrombosed after carotid ligation. This can be established by routine postligation arteriography. Is there a critical per cent of lowering of mean pressure at which thrombosis within the aneurysm will occur routinely? Are there other factors which may be altered sufficiently to promote thrombosis within the aneurysm only?

The percentage of reductions of pressure to afford protection against rupture must vary with every aneurysm and must be different in those patients who have hemorrhage and those who have not. Is there an exact percentage of reductions of mean pressure or of reduction of systolic pressure which will relieve the symptoms and improve the signs? A large series of cases is necessary to enable one to answer these questions.

SUMMARY

The different results that theoretically may follow carotid ligation in the treatment of intracranial aneurysms are discussed. The paucity of sufficient follow-up data and the necessity of extensive statistical studies are stressed. For the purpose of establishing criteria for the prediction of the outcome of carotid ligation, 14 patients were studied by means of pressure recordings from the internal carotid artery, preceding and after occlusion of the different carotid arteries, as well as by arteriography with compression of the contralateral internal carotid artery. This study seemed to indicate that when the anterior collateral circulation through the circle of Willis was found to be deficient with arteriography, the mean pressure in the internal carotid artery showed a fall of 55% or more of the original mean value after occlusion of the internal carotid artery or combined occlusion of the common and external carotid arteries. Most of the complications following carotid ligation, however, occurred in the patients who showed a fall of mean pressure of 65% or more upon the outlined occlusion, or a fall of the systolic pressure of 70% or more of its original value. The reliability of these studies as a means of prophesying complications may, however, be seriously hampered by the occurrence of a fall in the general blood pressure or of local spasm after carotid ligation, and two patients are presented who demonstrate these effects. Use of the Selverstone clamp, which permits quick release of the carotid occlusion, prevented permanent sequelae in those patients who showed complications.

In two patients pressures in a cortical branch of the middle cerebral artery were recorded at the same time as pressures in the internal carotid artery on the same side. Occlusion of the carotid arteries resulted in a fall in pressure in the cortical artery of almost equal degree to that in the internal carotid artery. These records indicate that even the peripheral cortical circulation can be profoundly influenced by carotid ligation.

16. Shenkin, H. A.; Cabieses, F.; van den Noordt, G.; Sayers, P., and Copperman, R.: J. Neurosurg. **8**:38-45, 1951.

RELUCTANCE TO MOVE PARETIC MUSCLES

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THE EXPERIENCE to be described happened to me and is reported in the interest of accurate diagnosis.

The episode followed voluntary loss of weight. After sitting for some minutes with the right leg crossed over the left knee, I found suddenly that the muscles of elevation of the right foot were almost entirely paralyzed; foot drop was almost complete. Loss of sensation and disagreeable paresthesias involved parts of the foot and leg and could not be clearly demarcated subjectively.

It was plainly necessary to try elevating the foot to learn the extent of damage. The attempt to do so proved to be extremely uncomfortable.

Because of this discomfort I was very reluctant to try to elevate the foot. It took a few seconds to overcome the reluctance; then the foot was raised. It moved through only a small part of its normal arc; how much of the limitation of motion was due to paralysis and how much to reluctance could not be determined. The discomfort and reluctance were so severe that in an untrained patient they might have produced false results in the examination of strength. For this reason I am reporting the observation.

The nature of the discomfort is hard to define. It might have resulted solely from the considerable effort required to contract such suddenly weakened muscles. It might have been connected in some obscure way with the sensory loss, which, because of the loss of position sense, made foot maneuvering all the more difficult.

Another point of interest is that roughly 90% recovery occurred in about five minutes. The remaining increment of recovery took an unmeasured but long (several months) time.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

STRUCTURAL AND FUNCTIONAL ADJUSTMENTS FOLLOWING REVERSAL OF THE EMBRYONIC MEDULLA IN AMBLYSTOMA. S. R. DETWILER, J. Exper. Zool. **116**:431 (April) 1951.

End-for-end reversal of the embryonic medulla was performed in Amblystoma larvae at Stages 25 and 27. The morphologic results were studied at Stage 46 by comparing samplings of volumes and cell counts from the cephalic end and the caudal end of the medullas with similar samplings from normal medullas of corresponding age. The functional ability of the surgically treated animals was determined by their swimming scores.

The morphologic-regulation capacity of medullas reversed successively through Stages 22 to 25, inclusive, appeared to be as extensive as that of medullas reversed at Stage 21, at which time Detwiler (1949) found that the reversed structures were almost normal. However, at Stage 25, in spite of a remarkable gross morphologic regulation, the swimming scores of the larvae were much lower, indicating a lack of functional readjustment, probably due to deficiencies in the intimate structure of the medulla. The irregularity of the swimming pattern suggested that reversal at Stage 25 inflicted severe disturbances in the motor tegmental nucleus, which normally regulates the motor activities of the medulla and cord.

When the medulla was reversed at Stage 27, morphologic regulation was only partly achieved, for, although the general shape of the medulla approached normal, there was less size contrast between the anterior and the posterior end. There was also less contrast between the volume and the cellular content at the cephalic and the caudal region. However, since the caudal portion of the reversed medulla was smaller than the anterior portion, some regulation had been achieved. Functional regulation was less in larvae operated on at Stage 27 than in those with medullas reversed at Stage 25.

The ears which developed after reversal at Stage 25 were variable and usually abnormal. In the majority of cases of reversal at Stage 27, the ears developed with completely reversed asymmetry. It would appear that at Stage 27 all the ear-forming material was restricted to the ectoderm, which was reversed with the medulla.

REID, New Brunswick, N. J.

NEOFORMATION OF CELLS OF PREGANGLIONIC TYPE IN THE CERVICAL SPINAL CORD OF THE CHICK EMBRYO FOLLOWING ITS TRANSPLANTATION TO THE THORACIC LEVEL. PAUL SHIEH, J. Exper. Zool. **117**:359 (July) 1951.

Preliminary extirpation studies of the spinal cord in chick embryos showed that the cervical portion of the cord begins at the 5th somite and ends at the 16th somite. The first 4 somites disappear, and the level of somite 16 of the early embryo corresponds to spinal cord segment 12.

Transplantations of the cervical cord segments of embryos of 9 to 25 somites (28 to 50 hours) to the thoracic levels were performed. A degeneration process occurred in the transplanted cervical cord at 4½ to 5 days of incubation that was identical with the process in the normal cervical cord at the same stages. In the caudal parts of the transplanted cervical cord appeared cell columns or scattered cells of preganglionic character which have no equivalent in the normal adult cervical cord. In respect both to their mediodorsal position and their neurites, which leave the cord by the ventral roots, these cells resembled the preganglionic columns of Terni, which are characteristic of the thoracic cord. Rami communicantes were present at the same levels at which these columns were found, and in a few instances fibers were traced from cells through these rami to the sympathetic ganglia.

Within the spinal cord, the neurites of these preganglionic cells took either a "typical" course ventrad and then laterad or an "atypical" course, turning first laterad and then ventrad, toward the ventral root. The typical cells appeared to be quantitatively better developed than the "atypical" cells. The cells of preganglionic type were differentiated only caudal to segments 5 or 6 of the transplants of cervical cords. They never appeared in the first four segments.

The motor system in the transplanted craniocervical portion of the cord and lower part of the medulla followed its normal, typical pattern. In many instances the nerves emerging from the transplant contributed to both limb plexuses, or to the lumbosacral plexus only, of the host.

REID, New Brunswick, N. J.

EFFECT OF INJURY ON DENERVATED UNAMPUTATED FORE LIMBS OF AMBLYSTOMA LARVAE. CHARLES S. THORNTON and DAVID W. KRAEMER, J. Exper. Zool. **117**:415 (Aug.) 1951.

The left forelimb of Amblystoma punctatum larvae (25 to 40 mm. in length) was denervated by cutting the nerves of the brachial plexus. Subsequent nerve resections made at 7- to 12-day intervals kept the limb denervated. During the first denervation the left forelimb was injured by crushing (without producing an open wound) or by perforating an area several times. In some limbs the injury was applied close to the wrist, while in others the injury was just distal to the upper arm, near the elbow. In each animal the normally innervated (right) limb received the same type of injury and served as a control. Records of the changes in the limbs were made by photographs and camera-lucida drawings.

Denervated limbs were found to regress extensively when a localized area of the limb was injured, whereas the normally innervated (control) limbs recovered quickly from similar injuries. In the majority of the denervated, injured limbs, regression was more rapid and extensive at distal limb levels than at proximal ones. It was found that in order to stimulate regression the injury must include the internal limb tissues, for a skin wound alone was ineffective. If the limb was denervated one week after the injury, no regression resulted.

After reinnervation only those limbs in which the digits were completely regressed could regenerate. If the digits persisted, even in an extensively regressed limb, the reinnervated limb did not regenerate. Thus, regeneration was dependent on the undifferentiated condition of the distal tip.

REID, New Brunswick, N. J.

RECONSTITUTION OF THE URODELE SPINAL CORD FOLLOWING UNILATERAL ABLATION: I. CHRONOLOGY OF NEURON REGULATION. HOWARD HOLTZER, J. Exper. Zool. **117**:523 (Aug.) 1951.

Unilateral (right side) extirpation of the third, fourth, and fifth segments of the spinal cord was performed in four species of urodeles—Amblystoma punctatum, A. opacum, A. tigrinum, and Triturus torosus. For reference purposes, the animals were divided into four groups, depending on age (Harrison's) at the time of operation: Group I, Stages 18 to 24; Group II, Stages 25 to 32; Group III, Stages 33 to 42; Group IV, Stages 43 to 20 mm. (free-feeding larvae). Of 400 animals treated surgically, 225 were studied histologically.

Restitution of the third, fourth, and fifth spinal cord segments was achieved by mobilization of cells across the midline from the intact half. Analysis of mitotic activity revealed that (1) the intensity of mitotic activity declined from the tail bud onward; (2) proliferation was progressively limited to the dorsal portions of the cord; (3) neuroblasts that had left the neural epithelium might still migrate and divide.

Histological detail in the restored half was shown to be a function of the source of the cells and the age of the embryo at the time of operation. In early stages cells of the motor outer mantle were present if the sheet of cells was formed from the intact floor plate, but were absent when the cells came from the roof plate of the intact side. It was found that the capacity of the intact half to supply the various cell types declined with age of the embryo at operation in the following order: (1) motor outer mantle, very early neurula; (2) sensory outer mantle, middle neurula; (3) ventral internuncial mass, Stages 33 to 36; (4) dorsal internuncial mass, Stages 37 to 40. However, the capacity for morphogenic regulation was retained throughout Stages 38 to 40.

Holtzer concludes that the early neural tube is composed of strains of neuroblasts whose capacity for differentiation is strictly circumscribed. Neuroblasts of the alar plate may form only sensory outer mantle and internuncial cells, whereas motor outer mantle cells are exclusive products of the ventralmost basal plate. Holtzer also concludes that, although the medullary system is of a mosaic nature, its subsystems are capable of limited differential hyperplasias. This capacity of the spinal subsystems was demonstrated by their normal differentiation, which was independent of the condition of neighboring subsystems.

Efferent roots of reconstituted cords displayed normal segmentation, which in the early groups indicated the presence of ipsilateral motor cells. In older groups the efferent roots sometimes arose from contralaterally located motor cells or the ipsilateral internuncial cells.

REID, New Brunswick, N. J.

FURTHER OBSERVATIONS ON MOTOR RESPONSES OF AMBLYSTOMA LARVAE FOLLOWING TRANSPLANTATION OF PRIMARY BRAIN SEGMENTS. S. R. DETWILER, J. Exper. Zool. **119**:189 (March) 1952.

Three different brain combinations were brought about by grafting primary segments in embryos of Stage 21 (just-closed neural folds): (1) substitution of embryonic hindbrain by a supernumerary forebrain, (2) replacement of mesencephalon by a supernumerary forebrain, and (3) substitution of the forebrain by a supernumerary mesencephalon. A quantitative method previously described by Detwiler (1946) for determining the motor capacity by swimming tests was the criterion of function.

Larvae in which the forebrain replaced the medulla and in which there was no nervous connection of the graft with the intact mesencephalon were functionally forebrain-spinal animals. Such larvae made low swimming scores and showed considerable irregularity in their swimming, owing to the loss of the motor tegmental nucleus.

Animals in which the midbrain was replaced by a forebrain made slightly higher scores than did those with midbrain replaced by spinal cord (Detwiler, 1948).

When the forebrain was replaced by a supernumerary mesencephalon, the motor scores of these larvae with two midbrains exceeded the scores of the controls throughout all the stages tested (up to Stage 46).

The results of these experiments, combined with those previously published by Detwiler, establish the fact that the spinal mechanisms for swimming, which are autonomous in the earliest stages, fall under the influence of the higher centers at Stage 40 to 42. The great importance of the midbrain was shown by the acceleration in motive power in Stages 44, 45, and 46, when a supernumerary midbrain replaced the forebrain.

From the results of all experiments, Detwiler concludes that the midbrain is most indispensable for the maintenance of normal swimming and that the forebrain is the least indispensable for this function. However, the medulla serves as a coordinator and regulator. For a greater understanding of these physiological results, a more detailed study of the intimate structural connections, with use of specific nerve stains, is necessary.

REID, New Brunswick, N. J.

RECONSTITUTION OF THE URODELE SPINAL CORD FOLLOWING UNILATERAL ABLATION: II. REGENERATION OF THE LONGITUDINAL TRACTS AND ECTOPIC SYNAPTIC UNIONS OF MAUTHNER'S FIBERS. HOWARD HOLTZER, J. Exper. Zool. **119**:263 (March) 1952.

Unilateral removal of both gray and white matter of the right side of the brachial spinal cord in urodele embryos was performed at various stages (Harrison's). Depending on the age at time of operation, the larvae were divided into four groups: Group I, Stages 18-24; Group II, Stages 25-32; Group III, Stages 33-42; Group IV, Stages 43-20 mm. Histological examination of over 100 larvae stained by the silver technique of Bodian was made 8 weeks to 10 months after operation. Only the terminal condition of the regenerated fibers will be reported.

Although unilateral ablation of the prospective brachial spinal cord in the neurula involved removal of approximately one-half the neural crest, the regulation of the remaining crest cells resulted in essentially normal spinal ganglia, pigment, and sheath cells.

Medially regenerated dorsal roots moved toward the dorsal aspects of the marginal areas and usually entered the sensory funicular areas directly. Entrance of the dorsal roots into motor funiculi was followed by dorsal deflection of the fibers in the marginal area and resulted in reestablishment of proper topographical relationships.

Functionally, the regenerated dorsal roots activated the spinal coordination centers. Ipsilateral cutaneous sensibilities were always restored. When the right root entered the left sensory funiculus, stimulation of the right limb elicited responses, but in the left limb.

In many cases regenerated longitudinal fibers were not applied to the gray matter. Such isolated tracts indicated that the posterior elongation of motor funicular fibers and the development of ascending and descending sensory funicular fibers were independent of local surface conditions in the mantle.

Observation of the site of origin and point of reentry of these isolated cables into the white matter showed that the motor fibers tended to associate with the ventral, and the sensory fibers with the dorsal, aspects of the marginal areas.

The regenerated Mauthner axon, especially in the early ablation groups, appeared to be responding discriminatively to microscopic cues in the surroundings by (1) coursing in its normal location posterior to the region of operation; (2) returning to proper position after running in an isolated cable, and (3) running with the normal, contralateral M-axon after a secondary decussation in the region of ablation. Although it behaved atypically in many instances—often bifurcating, running anteriorly, or coursing through the gray matter—the giant axon was usually located in the ventral funiculus, although in the peripheral reaches of the marginal area.

Ectopic Mauthner axons made synapses with motor and sensory outer mantle cells. Perikarya and nuclei of a single motor cell synapsing with two or more M-axons underwent considerable hypertrophy.

REID, New Brunswick, N. J.

WOUND HEALING AND REGENERATION IN EMBRYONIC SPINAL CORD OF AMBLYSTOMA PUNCTATUM. MAY B. HOLLINSHEAD, J. Exper. Zool. **119**:303 (March) 1952.

Embryos of Amblystoma punctatum were operated on at approximately Stage 15. Most of the operations consisted in removal of a bilateral strip of the spinal medullary plate with varying amounts of the adjacent neural ridges and underlying mesoderm. Some experiments involved only unilateral extirpation of spinal medullary plate either with or without the neural ridge.

When the gap made by bilateral extirpation of a portion of the spinal medullary plate with the adjacent neural ridges was too long to permit first-intention healing, there was a permanent gap in the central nervous system. The critical length of such a strip was between one-quarter and one-third the anteroposterior extent of the spinal neural plate and was influenced by the concomitant removal of the underlying mesoderm. When the underlying mesoderm was intact, an excision of the anterior third of the spinal medullary plate and ridge usually produced a permanent interruption of the neural tube. On the other hand, an excision including only the anterior one-quarter of the spinal neural plate was always followed by first-intention healing. Excision of the anterior quarter of the spinal neural plate with the substrate produced an interrupted cord in some cases. Extirpation of the anterior one-eighth of the spinal neural plate with underlying mesoderm always resulted in a continuous central nervous system.

Since ablation of the medullary plate leaving the adjacent ridges intact often failed to remove all presumptive spinal cord cells, these remaining cells produced a single neural tube, or double tubes, in the surgical area.

A single neural tube was more likely to result when the substrate was not removed, since the developing somites pushed the bilateral remnants toward the midline, where they fused.

The greater mechanical disturbance produced by removal of a very large mass of tissue (ectoderm and mesoderm) permitted the residual thin roof of the archenteron to protrude dorsally, thus interfering with fusion of the neural remnants and with first-intention healing. If the notochord was accidentally injured during the removal of the para-axial mesoderm, its herniation formed a similar mechanical obstacle to the formation of a normal spinal cord.

REID, New Brunswick, N. J.

CEREBRO-CEREBELLAR RELATIONSHIPS IN THE MONKEY. R. S. SNIDER and E. ELDRED, J. Neurophysiol. **15**:27 (Jan.) 1952.

Cerebrocerebellar relations were studied in the monkey by electrically stimulating various areas on the lateral cerebral surface and recording from the pial surface of the cerebellum (exclusive of the basal surfaces).

The authors found that cerebral sensory and motor Areas 3, 1, 2, and 4 project to the tactile areas of the cerebellum, i. e., the anterior lobe, the lobulus simplex, and paramedian lobules and immediately adjacent folia. Cerebral leg regions project to anterior points in the

contralateral anterior lobe and to posterior points in both paramedian lobules, whereas cerebral face regions project to posterior points in the anterior lobe and lobulus simplex and to anterior points in the paramedian lobules. Cerebral arm regions project to intermediate positions in both the anterior lobe of the cerebellum and the paramedian lobule.

The cerebral auditory receiving area projects laterally and medially to the lobulus simplex and surrounding folia. The cerebral visual receiving area (Area 17) projects to the lobulus simplex and surrounding folia, as do cerebral Areas 8 and 9. Areas 6 and 4s of the cerebrum project widely to contralateral Crus I and II and the lobulus simplex.

It was found that stimulation of Areas 7, 18, 19, and 22 failed to evoke cerebellar responses. It was not possible to explore basal surfaces and surfaces on the medial wall of the cerebrum for cerebrocerebellar projections.

ALPERS, Philadelphia.

Physiology and Biochemistry

DIRECT MEASUREMENT OF INTRAVASCULAR PRESSURE IN COMPONENTS OF THE CIRCLE OF WILLIS. B. M. BLOOR, G. L. ODOM, and B. WOODHALL, A. M. A. Arch. Surg. **63**:821 (Dec.) 1951.

Cervical or intracranial ligation of the carotid artery is commonly used for the treatment of intracranial aneurysms and vascular anomalies. The results of these procedures are unpredictable, and such operations may seriously endanger the cerebral circulation. The authors have attempted to obtain more accurate information by measuring the intra-arterial pressure in the carotid artery and its branches before resorting to permanent ligation. A 27-gauge needle attached to a Sanborn electromanometer can be introduced even into the intracranial arteries without undue danger of hemorrhage. The recordings thus obtained appear fairly accurate, although some dampening effect due to technical factors was noted.

In four cases (one of aneurysm of the anterior communicating artery and three of arteriovenous vascular anomalies) the systolic pressure was determined in the carotid artery and in intracranial vessels before and after vascular occlusion. Ligation of the carotid artery produced a constant fall of arterial pressure in the entire vascular segment; yet there was considerable individual variation. Whether the fall in pressure remains constant when vascular channels effecting cross circulation are impaired either by pathologic changes or by surgical ligation remains still to be proved.

LIST, Grand Rapids, Mich.

MANAGEMENT OF PAROXYSMAL HYPERTENSION FOLLOWING INJURIES TO CERVICAL AND UPPER THORACIC SEGMENTS OF THE SPINAL CORD. E. BORS and J. D. FRENCH, A. M. A. Arch. Surg. **64**:803 (June) 1952.

In patients with transverse lesions of the cervical or upper thoracic portion of the spinal cord, paroxysmal hypertension may be produced by various cutaneous or visceral stimuli applied below the level of the lesion. The hypertensive response is an autonomic spinal reflex phenomenon; it increases with caudad progression of the stimulation and is greatest in the anogenital zone. Temporary interruption of afferent pathways from the stimulated area by topical or conduction anesthesia prevents the rise of arterial pressure. When cystoscopy or transurethral resection becomes necessary in paraplegic patients, it is important to avoid the reflex hypertension by topical anesthesia of the urethra and bladder. Permanent relief from paroxysmal hypertension can be accomplished by bilateral posterior rhizotomy below the ninth thoracic segment. This operation was successfully used by the authors in seven cases. It should be performed only when the hypertension is severe enough to threaten the patient's life. Posterior rhizotomy is preferable to thoracolumbar sympathectomy because it avoids postural hypotension and respiratory complications due to surgical interference with the diaphragm.

In addition to the profound effect on paroxysmal hypertension, posterior rhizotomy produces many other physiologic changes; spinal reflex sweating, e.g., is diminished or abolished, but the pilomotor response not changed. Erection is abolished in most patients. The bulbocavernous reflex disappears at first, but may return, presumably because it is mediated by pathways arising above the level of the rhizotomy.

Bladder function remains in general unchanged, although increased detrusor activity has been observed in some instances. The spasticity of the lower extremities is not always eliminated because of the preservation of intersegmental reflex activity in the portion of the cord below the lesion but above the level of rhizotomy. LIST, Grand Rapids, Mich.

EFFECT OF ANTABUSE [DISULFIRAM] ON THE ELECTROENCEPHALOGRAM. E. W. BUSSE, A. H. BARNES, and F. G. EBAUGH, Am. J. M. Sc. **223**:126 (Feb.) 1952.

The electroencephalograms of 30 patients treated with disulfiram (antabuse®) for alcoholism were studied. Patients with normal pretreatment records showed little or no change in their records. Records of borderline abnormality showed dysrhythmia after the patients had received disulfiram for some time. In clearly abnormal records the abnormalities were increased after the drug therapy, especially during the period of hyperventilation. BERLIN, New York.

NITROGEN AND POTASSIUM METABOLISM: THE REACTION PATTERN IN POLIOMYELITIS. A. G. BOWIE, F. M. MORGAN, and A. L. CHANEY. Am. J. M. Sc. **223**:532 (May) 1952.

Analysis of 17 cases of poliomyelitis with respiratory involvement indicated that the disease is divisible into an acute catabolic phase, a subacute catabolic phase, and an anabolic phase. During the acute catabolic phase there is urinary excretion of large quantities of nitrogen and potassium, indicative of protoplasmic breakdown. These high levels persist longest in patients with the severest paralysis. In the subacute catabolic phase there is a lower excretion of potassium and nitrogen. The anabolic phase is characterized by synthesis of protein, with positive balance of potassium and nitrogen. The decrease in serum albumin during the anabolic phase may lead to shock in severe poliomyelitis. High serum potassium in the acute phase may lead to ventricular fibrillation, while low serum potassium accentuates the weakness.

BERLIN, Mount Vernon, N. Y.

GASTRIC ULCER OCCURRING IN A PATIENT AFTER LOBOTOMY. V. W. LOGAN and BASIL B. BOBOWIEC, Ann. Int. Med. **36**:1093 (April) 1952.

Logan and Bobowiec report the case of a man who was discovered to have a chronic, non-healing gastric ulcer 10 months after bilateral frontal lobotomy had been performed for a psychosis of six years' duration. The patient was placed on the usual ulcer regimen with bed rest and soon became symptom-free. While the ulcer at first showed evidence of healing in early films, a larger crater was later revealed, although the patient remained symptom-free. A subtotal gastrectomy was performed and the lesion found on the lesser curvature. The patient made a satisfactory recovery and has had no symptoms since.

There is a considerable body of evidence that the frontal lobe exercises control over gastrointestinal function. A review of the literature reveals general agreement that ablation of the frontal cortex will result in increased gastric acidity and motility for an undetermined period after operation.

In the case here reported several causative possibilities occur. The ulcer may have been purely fortuitous and have borne no relation to the operation on the brain. It may have represented the recurrence of a previously healed gastric ulcer. The ulcer and its sluggish response to healing may, however, have been due to the influence of the lobotomy in causing hypersecretion, hypermotility, and hyperacidity. Thus, the stage was set for ulceration at the time when the patient's dependent needs, formerly satisfied by psychotic devices, were threatened by attempted return to a less psychotic, more realistic, and, consequently, more demanding life program. ALPERS, Philadelphia.

DETERMINATION OF STRUCTURAL PATTERNS IN THE SPINAL CORD OF THE CHICK EMBRYO STUDIED BY TRANSPLANTATIONS BETWEEN BRACHIAL AND ADJACENT LEVELS. BYRON S. WENGER, J. Exper. Zool. **116**:123 (Feb.) 1951.

Transplantation of the neural tube between brachial and adjacent levels (cervical or thoracic) was performed in chick embryos of 13 to 24 somites (2-day incubation age). These grafts underwent excellent histological and morphological differentiation and innervated the adjacent regions of the host.

The recognition of host levels was based on cellular patterns in the spinal cord, rather than on skeletal structures. These levels, in terms of the spinal nerve segments included, are as follows: cervical, 1-12; brachial, 13-17; thoracic, 18-22. The spinal cord pattern characteristic for each level was determined on the basis of presence, shape, and relative position of mesial motor columns, lateral motor columns, and the remainder of the mantle. The preganglionic columns of Terni were studied in one case.

In all experimental cases cell groups characteristic of a given level were found in grafts from that level and were always in the same relative positions, irrespective of the host level to which the grafts were transplanted.

Nerves which arose from cervical or thoracic spinal cord grafted to the brachial region were more slender than normal brachial nerves, but could form a completely normal brachial plexus pattern under the influence of the brachial periphery. Variations appeared to be due to disturbances in either graft or periphery resulting from the operation. Nerves from brachial spinal cord grafted to another level could produce nerve patterns typical for that level (thoracic) without forming a plexus. However, nerves from brachial-cord grafts had a high capacity for growth and frequently made abnormal, plexus-like anastomoses.

Wenger draws the following conclusions: 1. As early as the cervical, brachial, and thoracic levels of the chick spinal cord can be identified (by adjacent somites), their respective cell types and patterns of cellular arrangement may be determined. 2. On the other hand, plexus patterns, as well as patterns of more distal peripheral distribution, are imposed upon nerves by surrounding tissues. 3. Wing movements typical of normal chick embryos of the same age (8 and 9 days) can be produced by nerves from the cervical or thoracic spinal cord. 4. Segmentation of the spinal cord in the chick appears to be dependent on mesodermal segmentation.

REID, New Brunswick, N. J.

SELECTIVE GROWTH STIMULATING EFFECTS OF MOUSE SARCOMA ON THE SENSORY AND SYMPATHETIC NERVOUS SYSTEM OF THE CHICK EMBRYO. RITA LEVI-MONTALCINI and VICTOR HAMBURGER, J. Exper. Zool. **116**:321 (March) 1951.

Small pieces of mouse sarcomas 180 or 37 (from the Jackson Memorial Laboratory, Bar Harbor, Maine) were grafted at the base of the wing bud or leg bud (between the limb bud and the somites) of 2½ to 3-day chick embryos. The tumors grew and invaded adjacent tissue, especially the mesenephros. The following responses of the nervous system to these tumors were observed:

The motor fibers and fibers from the early differentiating ventrolateral cells of spinal ganglia which reached the tumor at the incubation age of 5 to 6 days failed to enter it. These fibers either bypassed the tumor or were blocked by it. When the fibers were blocked, regressive changes occurred in the spinal ganglia, viz., degeneration of ventrolateral cells and reduction in the mitotic activity.

On the other hand, at 7 days of incubation large nerve bundles invaded the tumors, while at 11 days of incubation the density of nerves in the sarcomas exceeded that of any normal tissue at any embryonic stage. This beginning of nerve ingrowth coincided with the beginning of the differentiation and of hyperplastic growth in the paravertebral sympathetic-chain ganglia and in the group of late-differentiating, mediodorsal cells in the spinal ganglia. Evidence was given that the paravertebral sympathetic ganglia and the mediodorsal cells of the spinal ganglia supplied nerves to the tumor, whereas the ventrolateral cells of the spinal ganglia and the motor cells were refractory.

Prevertebral sympathetic ganglia, particularly sympathetic cells derived from the primordium of the adrenal medulla, participated in the nerve supply to the tumor.

The hyperplastic and hypertrophic responses of the sympathetic and spinal ganglia were more striking than those observed under other experimental conditions, reaching maxima of 600% for the sympathetic ganglia and of 250% for the spinal ganglia. This increase in size was due mostly to cellular hypertrophy, and, to a lesser extent, to an increase in cell numbers. There was an acceleration of the differentiation process in sympathetic ganglia and in the mediodorsal cells of the spinal ganglia.

The nerve fibers in the tumors were found to end abruptly, without making synaptic connections with neoplastic cells.

The authors conclude that sarcomas 180 and 37 produce specific growth-promoting agents which stimulate the growth of sympathetic and of sensory mediodorsal cells and fibers of spinal ganglia, but not of motor cells or of sensory ventrolateral cells of spinal ganglia.

REID, New Brunswick, N. J.

HISTOCHEMICAL STUDY OF CHOLINESTERASE DURING FORMATION OF THE MOTOR END PLATE OF THE ALBINO RAT. CARL KUPFER and GEORGE B. KOELLE, J. Exper. Zool. **116**:397 (April) 1951.

Manometric determinations of cholinesterase in a series of homogenates from the forelimbs of fetal rats (14 to 23 days gestation) revealed that the earliest appearance of significant amounts in the skeletal muscle occurred at about the 16th day of fetal life. Others (Straus and Weddell) have reported that the 16th day of fetal life marks the onset of neuromuscular excitability, although at this stage there are no visible motor endings within the muscle cells. Histochemical studies, with a precipitated copper sulfide method, showed that at the 16th day of fetal life the enzyme was localized chiefly on the surface of specialized muscle nuclei. Histological preparations stained with the silver-pyridine technique or with a modified gold chloride method demonstrated that the motor nerve fibers did not establish endings within the muscle cells until the 21st to the 22nd day of prenatal life.

The specialized muscle nuclei, upon the surfaces of which the cholinesterase was chiefly localized, were found in successive stages to aggregate at one locus within each muscle cell at approximately the same level as in the adjacent fibers. Such configurations were first clearly seen at birth (21 to 22 days) and were essentially indistinguishable from the adult pattern by the fifth day post partum. From the present study, the authors conclude that the cholinesterase activity is mainly associated with the specialized muscle nuclei of the sole plate.

REID, New Brunswick, N. J.

CENTRIPETAL PATHWAYS WITHIN THE SPINAL CORD FROM THE BLADDER. P. W. NATHAN and MARION C. SMITH. J. Neurol., Neurosurg. & Psychiat. **14**:262 (Nov.) 1951.

Nathan and Smith investigated the location within the human spinal cord of centripetal pathways from the bladder and the urethra. The material studied consisted of 27 patients with lesions of one or both anterolateral columns of the spinal cord and of three (control) patients in whom these regions were intact. The investigation was both clinical and histological.

The location within the spinal cord of man of the various pathways subserving (*a*) the sensation that the bladder is full, giving rise to the desire to micturate, and (*b*) the sensation of pain from the bladder, urethra, and lower end of the ureter, and the sensation of temperature from the urethra was found to be within the spinothalamic tract, on the surface of the cord opposite the dorsolateral process of the anterior horn. The various pathways subserving touch and pressure sense or tension from the urethra lie within the posterior column.

ALPERS, Philadelphia.

NEWLY DESCRIBED REFLEXES OF THE GLUTEAL REGION. J. DALMA, Prenza méd. argent. **39**:449 (March 7) 1952.

Dalma describes three reflexes in the gluteal region which he says have not been described previously. The gluteus maximus reflex is obtained by percussing the tendon of the muscle along its insertion into the sacral bone, with the patient in ventral decubitus. The reflex response, which is a contraction of the homolateral gluteus maximus muscle, was obtained in all subjects who had no neurologic disease. In 10% of the patients examined the contralateral gluteus maximus also contracted. It is a tendon reflex whose afferent arc passes through the fifth lumbar segment. Previous gluteal reflexes described by Bechterew (1908), Haskovec (1911), and Grossmann (1929) are in the author's opinion variants of the same gluteus maximus reflex. The so-called clonus described by Joffroy and others is really a hyperreflexia of the gluteus maximus encountered in disease of the pyramidal tract. This clonus has never before been elicited with the percussion hammer. It has been found by the author in cases of spastic

paraparesis. Absence of the gluteus maximus reflex is of value in localizing lesions at the fifth lumbar level, particularly when there are no sensory changes. It is also absent with lesions of the inferior gluteal nerve.

The gluteus medius reflex is obtained by percussion of the upper outer quadrant of the buttock in the region of the insertion of the gluteus medius and of the insertion of the tensor fasciae latae into the iliac crest. A contraction of the gluteus medius is seen, and in some cases of the tensor fascia lata as well. The segments involved are the fourth lumbar to the first sacral. This reflex is sometimes not readily obtained in stout subjects. It has never been described before. A reflex was described by Schüller in which contraction of the gluteus medius is obtained by percussing the distal insertion of the muscle into the external condyle of the femur. Reflex contraction of the tensor fascia lata by percussing its tendinous insertion into the iliac crest has been known for a long time. The gluteus medius reflex is absent in lesions of the superior gluteal nerve.

The femoral-gluteal reflex has never been described before. It is obtained by vigorous percussion of the medial aspect of the superior part of the posterior aspect of the thigh just below the gluteal fold. Percussion at this point causes contraction of gluteal muscles on both sides in 10% of cases. At times the muscles in the thigh itself may also contract. The author found the reflex present in 60% of poorly nourished patients in a psychiatric hospital. He suggests that this hyperreflexia may result from hyperexcitability of neural mechanisms involved as a result of malnutrition.

The author defends his theory that these reactions are true tendon reflexes by pointing to the fact that they are elicited by stimulation of tendons rather than of muscles; the presence of clonus with upper motor neuron disease is also evidence against a purely muscular response. Tracings obtained from the muscle by means of an electroencephalograph, according to the technique of Hoffmann, also prove the reflex nature of these reactions.

N. Savitsky, New York.

Neuropathology

Clinical Significance, Histopathology and Classification of Cerebral Swelling. I. M. Scheinker, Neurology **2**:177 (May-June) 1952.

"Cerebral swelling" is the term proposed to denote the gross appearance of a brain characterized by a local or diffuse increase in bulk of one or both hemispheres. The condition referred to grossly as cerebral swelling is represented microscopically by three types of histopathologic change described as tumefaction, edema, and liquefaction.

Pertinent histologic findings characteristic of cerebral tumefaction are (1) parenchymatous changes, with evidence of swelling of the nerve fibers, myelin sheaths, glia, and, particularly, oligodendroglia, and (2) vascular alterations, confined to the small veins and capillaries, characterized by congestion and stasis and by swelling and degeneration of the endothelial cells. These changes are predominant in the white matter and seldom extend into the gray substance.

The essential histologic findings in cerebral edema are (*a*) alveolar or sieve-like appearance of the nerve tissue, (*b*) maximal distention of the perivascular and pericellular spaces, (*c*) signs of venous congestion and stasis, and (*d*) evidence of degeneration and necrosis of the endothelium of the capillaries.

Cerebral liquefaction is characterized by (1) large accumulations of serous fluid within the central white matter; (2) diffuse, and almost complete, disintegration of the nerve fibers and myelin sheaths; (3) regressive glial changes (Alzheimer's ameboid glia), and (4) degenerative alterations of the vessel walls.

Scheinker points out that fundamentally these three conditions represent different stages of the same biologic process; occasionally they may merge one with another.

The role of cerebral swelling in the production of midbrain hemorrhages is emphasized. These are believed to be perivenous in origin, and to be caused by an extreme degree of venous congestion, resulting from compression and strangulation of the veins of the herniated midbrain.

The author draws attention to the significance of unilateral cerebral swelling in the production of transtentorial herniation of the brain stem. Clinical observations, pathologic lesions, and experimental findings in this condition are reviewed. Transtentorial herniation of the

brain stem presents a grave hazard for the clinician and neurosurgeon. Lumbar puncture and pneumoencephalography must be interdicted if the existence of the herniation of the brain stem has been clinically recognized or suspected. In view of the gravity of the clinical symptoms, an attempt to distribute pressure more evenly by means of the establishment of ventricular drainage or by means of section of the free edge of the rigid tentorium may be a lifesaving measure, pending final, and more radical, treatment.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

MENTAL CHANGES ASSOCIATED WITH HYPERPARATHYROIDISM. T. E. FITZ and B. L. HALLMAN, Arch. Int. Med. **89**:547 (April) 1952.

When the classic clinical picture of hyperparathyroidism is present, the diagnosis is usually readily made. The most bizarre clinical pictures are produced when the calcium levels are extremely high, that is, when the picture of calcium poisoning is present. This condition has been referred to as "parathyrotoxicosis."

Fitz and Hallman report two such cases of hyperparathyroidism with pronounced mental changes as their primary and major symptoms. The classic changes, such as demineralization of the bones, fractures, bone pains, and extreme renal calcinosis, were not present. In both cases the mental disturbances produced such an unusual picture that the diagnosis was overlooked for several months.

Operation was performed in both cases, and parathyroid adenomata were removed, with rapid clearing of all mental symptoms. The mechanism of this psychosis is not known, although nervous and mental disorders have been observed in patients and in animal experiments when the serum calcium level was elevated.

ALPERS, Philadelphia.

TRIAL LOBOTOMY BY PREFRONTAL BLOCK. E. EDUARDO KRAPF and JULIO H. LYONNET, Prensa méd. argent. **38**:2886 (Nov.) 1951.

Souleirac and Barbizet, in 1946, and Lindsay, in 1950, showed that guinea pigs could tolerate injection of procaine directly into the brain. This was confirmed by Lindsay, in 1950, and Mandel, in 1951, in human beings. The authors report three cases of psychoses in which procaine was injected into the frontal lobe. There was definite improvement, lasting five to seven days, after which previous excitement and other psychotic manifestations returned. This improvement justified a prefrontal lobotomy according to the technique of Freeman and Watts. In each case more persistent improvement was noted after the operation. Immediately after the procaine infiltration a major seizure was noted in one of the patients. Four centimeters of 2% procaine hydrochloride was injected into the frontal lobe, 1 cc. into each of four trephine holes. The authors suggest the possibility of improvement in some cases with procaine injection alone.

N. SAVITSKY, New York.

Meninges and Blood Vessels

OPTOCHIASMATIC ARACHNOIDITIS WITH THE FOSTER KENNEDY SYNDROME. RENATO SEIDENARI, Riv. oto-neuro-oftal. **26**:438 (Sept.-Oct.) 1951.

Seidenari reports the case of a 34-year-old member of a religious order who was known to have right optic nerve atrophy. For about a year he had complained of headaches, especially on exposure to the sun. The author found greatly diminished vision in the right eye, which was not improved by glasses. Examination showed pallor of the right disk, especially on the temporal side; blurring of the nasal edge of the right disk and slight congestion of the retinal veins, and papilledema in the left eye, with no significant diminution of vision. There was a small central scotoma in the right eye. The left field was normal. Carotid arteriography revealed no abnormality. Cisternal encephalography showed changes in the basilar cistern and in the subarachnoid spaces in the frontal region. One month later vision in the right eye was decreased, and papilledema had increased. A right frontal craniotomy was done, and arachnoidal lesions around the optic nerves and optic chiasm were found and liberated. Four

weeks after operation there was notable improvement of vision in the right eye, and the papilledema had disappeared in the left eye. There was still a relatively small scotoma for color in the right eye.

The disappearance of the papilledema and the improvement of vision in the right eye after the operation indicate that the optochiasmatic arachnoiditis was the cause of the Foster Kennedy syndrome.

N. Savitsky, New York.

Cerebral Revascularization by End-to-End Anastomosis of the Jugular Vein and the Carotid Artery. J. H. Lyonnet, D. Brage, and Roberto Geseli, Prensa méd. argent. **38**:2781 (Oct. 26) 1951.

The authors report 11 cases in which an attempt was made to increase the circulation of the brain by end-to-end anastomosis of the carotid artery and the jugular vein. Operation was done on the right side in all cases. All previous operations had been performed by Beck's method ("lateral anastomosis"). The operation was done in two cases of schizophrenia, three of mental deficiency, five of epilepsy with mental changes, one of a psychosis the nature of which was unclear, one of schizophrenia, and one of mental deficiency with epilepsy. In two cases in which angiography was successful after the operation the venous sinuses filled amply, evidence of the pouring into the intracranial venous system of arterial blood. The thrill and bruit at the site of operation was noted in each case after the second week. In a few cases contralateral pyramidal-tract signs were noted, but never motor weakness. The spinal fluid pressure was increased in all cases after the operation. Rose-colored spinal fluid was noted in one case and frank subarachnoid bleeding in another. In nine cases papilledema was noted, being usually more pronounced on the contralateral side. In two cases vision became impaired, with prompt improvement after the anastomosis was interrupted. No significant effect on the neurologic and psychiatric conditions of the patients was noted. The operation is not recommended.

Nathan Savitsky, New York.

Cerebromeningeal Edema Due to Arterial Hypertension. R. Thurel, Arq. neuro-psiquiat. **10**:193 (June) 1952.

Diffuse edema of the meninges must be considered as one of the complications of arterial hypertension, in addition to softening, hemorrhage, and edema around focal cerebral lesions. The acute variant of acute meningeal edema, though rarer, presents a more distinctive clinical picture. The acute form is usually ushered in by severe pulsating headaches, nausea, vomiting, visual disturbances, torpidity and seizures; the neck soon becomes rigid, with the appearance of a Kernig sign and papilledema. A rapid onset, with progression paralleling the rise in blood pressure, favors the diagnosis. The spinal fluid pressure is high, and the protein content of the fluid may rise to 1,000 mg. per 100 cc., without cells; occasionally red blood cells are seen. The patient may die or may improve after lumbar puncture. Vision improves at first in one-half the visual field, indicating that amaurosis is probably due to cerebral involvement.

The subacute variant has a course and clinical picture which are very much like those of an expanding lesion. However, when diminution of vision appears, one often notes exudates in the macular region, in addition to retinal hemorrhage. It must always be borne in mind that hypertension and brain tumor may coexist. In one case in which air studies were made from below, a dilated ventricular system was present. The electroencephalogram helps in differentiation from tumor; in cases of cerebromeningeal edema diffuse bursts and slow waves are more likely to be encountered.

At necropsy the subarachnoid spaces are seen to be filled with large amounts of spinal fluid. The brain is increased in volume and appears congested. Histologically, one finds distention of the perivascular, and even the pericellular, spaces. The author calls special attention to the breaking up of myelin fibers and the compression of ganglion cells in the Gasserian ganglion and in some of the spinal root ganglia. Multiple small hemorrhages, usually bilateral, are found in the region of the thalamus and putamen and cannot be considered the cause of death. Hemorrhage and edema are noted especially in the retina.

The increase of fluid in the brain and meninges is due to a passage of plasma, water, and even whole blood through diseased blood vessels as a result of an increase in pressure in various

parts of the brain and eye. Such transudation is possible because the arteries and arterioles are diseased as a result of prolonged hypertension. The arteries show proliferation of connective tissue in the intimal layer and of the muscle tissue in the media. Vessels of the endocrine glands are not involved in this process.

In the acute forms the author advises phlebotomy, use of vasodilator substances, and lumbar puncture. In the subacute forms he suggests a low-salt regimen, use of diuretics, intravenous injections of magnesium sulfate, repeated lumbar puncture, and even subtemporal decompression if necessary. Further trials of the operative procedures suggested for arterial hypertension (removal of adrenal glands and splanchnicectomy) are advisable, in spite of inconstant results.

N. Savitsky, New York.

Carotid-Cavernous Sinus Fistula. B. J. Alpers, Arq. neuro-psiquiat. **10**:203 (June) 1952.

Alpers reports five cases, one of which was an unusual instance of bilateral aneurysm of the cavernous sinus—a carotid-cavernous sinus fistula on one side and a saccular aneurysm on the other. In three of the five cases the lesion was spontaneous in origin and in 2 it followed head trauma. In none of the five cases was pulsation of the eyeball found by inspection or palpation. Absence of pulsation is said to be characteristic of cases of spontaneous origin, but in this series it was absent in the two cases of traumatic origin. In one case exophthalmos was bilateral. Its occurrence in the opposite eye may be delayed for weeks or months. In four cases there was complete ophthalmoplegia on the affected side, and in one there was impairment only of upward and downward movement. In the first case, in addition to complete ophthalmoplegia on the affected side, there was almost complete paralysis of the extraocular muscles in the other eye except for slight lateral motion. Visual acuity was reduced in two of the three cases in which it was recorded. There was no optic atrophy or papilledema in this series, though in two cases the disk margins were blurred and in one of these the temporal side of the optic nerve had a grayish discoloration. Arteriography confirmed the presence of a carotid-cavernous sinus fistula in three of the five cases. In one case the condition cleared spontaneously. In four of the five cases the common carotid artery was ligated. In three of the four cases in which follow-up observations could be made the bruit disappeared. In these three cases there was also improvement of the exophthalmos and the movements of the eyeball.

Savitsky, New York.

Diseases of the Brain

Epidermoid Arising from the Petrous Portion of the Temporal Bone. E. D. Fisher and P. J. Vogel, Bull. Los Angeles Neurol. Soc. **16**:357 (Dec.) 1951.

Fisher and Vogel report the findings in the case of a woman aged 28 who presented the symptoms and signs of a lesion involving the middle fossa on the right side, in addition to those suggestive of a cerebellopontine-angle tumor. Roentgenograms indicated extensive erosion of the petrous pyramid and bony changes in the middle fossa and lesser wing of the sphenoid bone. A crescent-shaped line of calcification outlined the upper border of the tumor. Audiometric and vestibular tests suggested an angle lesion on the right. A large cholesteatoma, measuring 4 by 4 by 7 cm., which had extensively eroded the pyramid of the petrous portion of the temporal bone and occupied much of the middle fossa in front and the cerebellopontine angle behind, was removed surgically. The gross and microscopic appearance was characteristic of an epidermoid. This tumor is one of the largest cholesteatomas reported. Apparently, its origin was in the petrous portion of the temporal bone, which it destroyed and then spread into the anterior and posterior fossas. The patient made an excellent recovery and was free from symptoms and at work in two months.

Alpers, Philadelphia.

Brain Tumors in Children. Arthur B. Smith, Radiology **58**:688 (May) 1952.

Smith reviews the literature concerning brain tumors in children and adds 34 cases of proved cerebral tumors. Approximately one-sixth of all tumors of the brain occur in children under 15 years of age. Most of these occur in the younger age groups and are located chiefly below the tentorium cerebelli. The majority of the subtentorial tumors are highly malignant. The

commonest subtentorial tumor in children is the astrocytoma, which is benign and grows slowly, usually in one cerebellar hemisphere. If removal can be accomplished, it does not recur.

The medulloblastoma is the second in order of frequency. Medulloblastomas are commonest in boys from 3 to 6 years of age. Irradiation is the treatment of choice for cerebellar medulloblastoma, although it is not curative. Operative treatment rarely gives relief for more than six months, no matter how radical the operation. The striking improvement which is usually noted within 10 days of the beginning of x-ray therapy is of some diagnostic value, for other tumors in this region are not nearly so radiosensitive.

Ependymoma of the fourth ventricle is about one-third as common as medulloblastoma. Tumors of the cerebral hemispheres are uncommon in children. In the author's series, 11 tumors were supratentorial, and 23 were subtentorial. The supratentorial tumors usually occur in or around the third ventricle. Tumors around the third ventricle all produce increased intracranial pressure, and treatment is generally unsatisfactory. Tumors of the pons and medulla are usually highly malignant, infiltrating gliomas, which are resistant to all forms of treatment.

Plain films of the skull reveal abnormality in more than half of the cases of brain tumor in children, whether by evidence of increased intracranial pressure, abnormal calcification, or bone erosion. Ventriculography was performed in 16 of the author's cases. In 12 of these 16 cases the diagnosis of a localized mass was made from the x-ray films. Dilated ventricles were found in the other four cases.

WEILAND, Grove City, Pa.

CHOLESTEATOMAS OF THE CEREBELLO-PONTINE ANGLE. H. OLIVECRONA, Acta psychiat. et neurol. **24**:639, 1949.

In a review of 29 cholesteatomas found by Olivecrona at various sites, 7 in the cerebellopontine angle seemed of special interest because 50% were associated with a typical syndrome. Trigeminal neuralgia involving the third division was frequent in young subjects, of about the age of 3 years. The pain resembled that of the tic douloureux of older persons. Neurologic findings were lacking except in one case, in which the corneal reflex was diminished. No changes were seen in roentgenograms of the skull. The diagnosis was made by encephalography, which usually showed displacement of the cisterna pontis and the cisterna ambiens. The tumor could be removed readily, but the capsule might be adherent to the basilar artery or other vascular structure. Recurrence is considered rare even if the capsule is not removed. There has been no case of recurrence of angle tumors of this type even after an observation period of 10 years. In two cases the trigeminal root was partially divided, with little sensory loss, and in another case it was sectioned completely. Tractotomy was performed in one case. The pain subsided in all the cases and did not recur.

PISETSKY, New York.

Diseases of the Spinal Cord

NON-NEUROLOGICAL LESIONS SIMULATING PROTRUDED INTERVERTEBRAL DISK. H. H. YOUNG, J. A. M. A. **148**:1101 (March 29) 1952.

The purpose of this presentation is to sound a word of caution concerning the diagnosis of protruded intervertebral disk. Young points out that lesions which cause low-back pain and pain in the leg are not always situated in the spinal column or the spinal canal.

Ten cases are presented in which the symptoms closely simulated those caused by protrusion of an intervertebral disk. An osteoid osteoma of the femur was present in four of the cases. One of the following lesions was present in the six remaining cases: glomus tumor of the leg, twisted ovarian cyst, multiple myeloma of the spinal column, eosinophilic granuloma of the pelvis, chondromyxosarcoma of the femur, and tuberculous arthritis of the sacroiliac joint.

ALPERS, Philadelphia.

News and Comment

AMERICAN ACADEMY FOR CEREBRAL PALSY

At the last meeting of the American Academy for Cerebral Palsy, held in Durham, N. C., Oct. 2 to 4, 1952, the following officers were elected:

Arnold Gesell, M.D., president; Meyer A. Perlstein, M.D., president-elect; Harry E. Barnett, M.D., secretary-treasurer.

ACTA PSYCHOTHEAPEUTICA, PSYCHOSOMATICA ET ORTHOPAEDAGOGICA

Starting Jan. 1, 1953, a new quarterly, entitled *Acta psychotherapeutica, psychosomatica et orthopædagogica,* will be published under the editorship of Franz Alexander (Chicago), Flanders Dunbar (New York), L. van der Horst (Amsterdam), H. Hanselmann, (Ascona), and J. Mulder (Leyden). The chief editors are E. A. D. E. Carp and B. Stokvis, both of Leyden, Netherlands. The editorial board comprises some 50 prominent representatives of the specific fields of study with which the journal will deal. The *Acta psychotherapeutica, psychosomatica et orthopædagogica,* being an international publication, will contain (original) contributions in the French, German, and English languages. Correspondence should be addressed to the editorial office: B. Stokvis, Psychiatrie University Clinic, Leyden-Oegstgeest, Netherlands. The publisher is S. Karger, Basel, Switzerland.

Books

Illegitimate Sonnets. By Merrill Moore, M.D. Price, $2.75. Pp. 125; illustrated. Twayne Publishers, Inc., 34 E. 23d St., New York 10, 1952.

Merrill Moore has given us another book of sonnets, and, like previous volumes, they are memorable. It seems to this reviewer that these sonnets are a little more complete, more rounded, than most of the previous ones. Some, while free in structure, are definitely romantic in content, and might be candidates for "The Golden Treasury," such as "Sleepy Water" and "Night is Filled With." Others have the typical Moore touch—the slightly oblique aspect, the sly innuendo, the tolerance of human vagaries that comes from listening to distressed and disturbed patients all day long. The reader might find himself more tolerant and understanding, too, by the time he has finished the book.

Morbus Alzheimer and Morbus Pick: A Genetic, Clinical and Patho-Anatomical Study. By Torsten Sjögren, Hakon Sjögren, and Åke G. H. Lindgren. Acta psychiatrica et neurologica. Supplement 83. Price, 25 Swedish crowns. Pp. 152, with 11 illustrations and 14 tables. Ejnar Munksgaards Forlag, Nørregade 6, Copenhagen K, Denmark, 1952.

Sjögren and his colleagues have added another study to their fine series of monographs on the genetics of neurologic disorders. The total number of probands in this study was 80, and extensive field investigations resulted in the discovery of 30 secondary cases. Of all the proband material, 36 were verified by histopathologic examination; 29, by air studies, and 15, only by clinical examination. Since there was apparently no intermarriage among the families, the authors calculated that the empirical prognosis in the risk period of 40 to 70 years was 16% in families in which one of the parents was affected, as against 2.5% for the sibs in families in which neither of the parents was affected. The likelihood of a multifactorial type of inheritance was greater for Alzheimer's disease (presenile sclerosis) than for Pick's atrophy. For the latter disease the hypothesis of a dominant major gene with modifying genes appears more acceptable. Furthermore, while differences between the two diseases are apparent only on pathologic examination, the average expectation of life was less than one-half that of a person of the same age in the normal population. While women were more commonly affected than men, the difference was not statistically reliable. Sjögren ends with the statement that the incidence of such disorders in the senium is higher than is commonly realized and that in Sweden there are roughly 500 contemporary living patients with these diseases.

Sjögren found more similarities than differences in the two clinical pictures. Lack of spontaneity was the outstanding phenomenon in 15 of 18 cases of Alzheimer's disease proved histologically and in 8 of 13 cases of Pick's disease. Then followed language disturbances, hypertonus, and facial paresis in a high proportion of cases of Alzheimer's disease, while hypertonus and disturbance of gait were uncommon in cases of Pick's disease. Dementia was severe in both types; convulsions were oftener observed in the former.

A curious circumstance noted by the authors was the difference in incidence of the two diseases in the two cities of Stockholm and Göteborg. Lindgren found only 2 cases of Alzheimer's disease in his Stockholm material, but 20 cases of Pick's disease, while in Göteborg a number of cases of Alzheimer's diseases were found, but no case of Pick's disease. The pathologic differentiation was very easy. The cerebral atrophy was diffuse in Alzheimer's disease and circumscribed in Pick's. Changes in the basal ganglia were regularly found in Alzheimer's disease, but in only one case of Pick's disease. Fibrillar condensation and argentophile plaques were found in great numbers in Alzheimer's disease, but not at all in Pick's disease. Ballooned cells were regularly found in Pick's disease, but none in Alzheimer's disease. Three aged patients with Pick's disease showed in addition histologic changes indicative of senile dementia.